Treatment related morbidity in breast cancer patients

A comparative study between sentinel lymph node biopsy and axillary lymph node dissection

Hans Rietman

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Stellingen

behorende bij het proefschrift

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Hans Rietman
Groningen, 15 juni 2005

1. Binnen de behandeling voor borstkanker is de okselklierdissectie de belangrijkste veroorzaker van armklachten. (dit proefschrift)

2. Vanwege de relatie tussen behandeling gerelateerde klachten van de bovenste extremiteit bij borstkanker patiënten en beperkingen in dagelijkse activiteiten en verslechtering van kwaliteit van leven, is het van groot belang deze klachten te voorkomen. (dit proefschrift)

3. De introductie van de poortwachterklier procedure (SLNB) is wellicht de belangrijkste chirurgische vernieuwing binnen de behandeling van borstkanker. (dit proefschrift)

4. In tegenstelling tot het optreden van fantoompijn bij arm- of beenamputaties, heeft dit fenomeen bij borstamputaties weinig tot geen klinische relevantie. (dit proefschrift)

5. Gezien het effect van behandeling gerelateerde armklachten bij borstkanker patiënten op kwaliteit van leven, dient integratie van psychologische ondersteuning binnen de somatisch gerichte behandeling standaard plaats te vinden. (dit proefschrift)

6. De methode van Sitzia verdient het de nieuwe gouden standaard te worden binnen de oedeem metingen. (dit proefschrift)

7. Promovendi die pas na het afronden van het proefschrift weer tijd vinden voor het gezin, hebben een verkeerde keuze gemaakt.

8. Vijf jaar geleden werd mij nieuwsgierig gevraagd of de 'botox' voor cosmetische doeleinden hetzelfde middel was als dat voor spasticiteit behandeling. Nu vraagt men het omgekeerde.

9. De tijd is nabij dat de valide topsprinter om een hightech prothesevoorziening zal vragen teneinde zijn record te verbeteren.
(Erica Terpstra dd 18-03-05 VRA Lustrum)

10. De gehandicapte patiënt van vroeger heet nu een persoon met mogelijkheden, maar ervaart veelal dezelfde maatschappelijke drempels.

11. De sirene van één ambulancewagen kan een eind maken aan de Samaritaanse houding in een hele Chileense stad.
(Ivan Illich; Grenzen aan de geneeskunde, 1978, Het wereldvenster, Bussum)

12. Gezien de verslechtering van motorisch functioneren, gepaard gaande met toenemende beperkingen in dagelijkse activiteiten en vermindering van kwaliteit van leven bij een grote groep borstkanker patiënten, is het vreemd dat deze patiëntengroep niet tot de doelgroep van de revalidatiegeneeskunde behoort.

Rijksuniversiteit Groningen

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Proefschrift

ter verkrijging van het doctoraat in de
Medische Wetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. F. Zwarts,
in het openbaar te verdedigen op
woensdag 15 juni 2005
om 16.15 uur

door

Johan Swanik Rietman

geboren op 6 januari 1960

te Almelo

Promotores:	Prof. W.H. Eisma
	Prof. Dr. H.J. Hoekstra
	Prof. Dr. J.H.B. Geertzen
	Prof. Dr. J.W. Groothoff
Copromotor:	Dr. P.U. Dijkstra

Beoordelingscommissie:	Mw. Prof. Dr. E. Lindeman
	Prof. Dr. R. Sanderman
	Prof. Dr. T. Wobbes

Paranimfen: Cees Buren

Rienk Dekker

The publication of this thesis is financially supported by:

OIM Stichting
D.H. Heijne Stichting en Basko Healthcare
De Stichting Beatrixoord Noord-Nederland
Afdeling Revalidatie UMCG
AB Medical PRS
Ipsen Farmaceutica BV
Guerbet Nederland BV
Novartis Oncology
Integraal Kankercentrum Noord-Nederland
Martini Ziekenhuis Groningen

Cover sculpture by Sjoukje Hiemstra
Cover design by Hans Rietman
Layout by Hans Rietman
Printed by Stichting C. Regenboog, Groningen, The Netherlands

ISBN 90-7711-3282

Voor mijn ouders

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CHAPTER 1

Introduction and outline of the thesis

Introduction

The incidence of breast cancer is generally increasing worldwide and especially in the developed nations. In the Netherlands is the current incidence already 127/100.000 women per year.[1] Some of this increase in incidence is attributable to earlier detection due to the availability of breast screening services for women, especially where mass population screening program's have been implemented.[2] One out of nine to ten women will develop today breast cancer, of which 70-80% will survive at least five years.[3,4] Most breast cancers occur in women over the age of 50 years, and the risk is especially high for women over the age of 60 years. Breast cancer in women under the age of 35 years is very uncommon.

Breast cancers are staged, just as all other malignancies, according to the TNM classification of malignant tumors in five groups.[5] The major alterations in the latest revision of the breast cancer staging was the regional lymph node classification of breast cancer. Supraclavicular lymph nodes were not longer staged as metastatic disease and the pathological assessment of the sentinel lymph node was incorporated in the pathological classification. The treatment of breast cancer is based on the extent of the disease, e.g. localized breast cancer (stages I and II), locally advanced breast cancer (stage III) or metastatic breast cancer (stage IV). Today, the treatment of breast cancer is mostly a combined treatment of surgery, radiation, chemotherapy and/or hormonal treatment.

Treatment for breast cancer

Today, two local treatment options are available for these patients; breast conserving treatment and modified radical mastectomy.

Breast conserving treatment consisting of breast-sparing surgery (local excision of the tumor or lumpectomy), axillary staging with sentinel lymph biopsy or axillary lymph node dissection, followed by radiation therapy in case of breast conserving treatment and axilla in case of extensive lymph node involvement.[6]

Modified radical mastectomy is an en bloc removal of the complete breast and the axillary lymph nodes with preservation of the pectoralis muscles.

The choice of breast conserving treatment or modified radical mastectomy depends mostly on the size and location of the tumor, the size of the woman's breast, certain features of the breast cancer, and how the woman feels about preserving her breast.

Radiation therapy of *the breast* in case of breast conserving treatment consist of radiation of the breast with a total doses of 50 Gy given in 25 fractions of 2 Gy during 5 weeks and, when indicated, a boost dose of 10-20 Gy.[6] Radiation of the *chest wall* is necessary when the surgical resection margins of the resected breast tissue are involved with tumor, or the breast tumor is classified as a T4 tumor, e.g. tumor

infiltration in the skin. *Regional radiation* is indicated when there are more than three positive axillary lymph nodes and or involvement of the apical lymph node. Radiation of chest wall or axilla consists of 45-50 Gy in 5 weeks as elective doses and in case of macroscopic remained tumor an additional dose of 15-20Gy, total dose of 60-70 Gy in 6-7 weeks in equivalent fractions.[6]

Diagnosis and treatment of the regional (axillary) lymph nodes

Aims of the treatment of the axillary lymph nodes are: optimal regional tumor control, optimal lymph node staging for the indication for adjuvant systemic and/or locoregional treatment. Besides this, axillary staging provides prognostic information. *Axillary lymph node dissection* (ALND) is therefore an important diagnostic, staging and treatment procedure.[7] This procedure consists of at least level I-II ALND with a minimum of 10-lymph nodes removed and examined.[8] ALND is associated with upper limb morbidity such as pain, numbness, lymph edema, weakness and impaired shoulder range of motion.[7,9-14] There is a need for less invasive surgical staging of the axilla.

Sentinel lymph node biopsy (SLNB) was introduced for staging of the axilla to reduce the number of unnecessary ALND's.[15] A sentinel node is the first lymph node to receive lymphatic drainage from a tumor. This novel approach involves lymphoscintigraphy and a minimally invasive surgical technique, and appears to allow the same information for staging and prognosis to be gathered with a limited morbidity. The purpose of lymphoscintigraphy for lymphatic mapping is to demonstrate the lymphatic drainage pathway of the tumor. There are two techniques to find the sentinel node during surgery: instrument-guided mapping and visually guided mapping.[16]

In the instrument-guided mapping, a gamma detection probe is used as a guide to the sentinel node after administration of a radioactive tracer. The radioactivity that remains in the node can be exploited to this end when surgery is performed within 24 hours. With the gamma probe, the location of the node can be determined through the intact skin.[16]

The other technique to find a sentinel node is with the aid of a vital dye, (isosulfan blue, patent blue®) which is injected in or around the tumor immediately prior to the operation. The area is massaged for several minutes to increase the lymph flow. Once the dye is taken up by the lymphatic system, it stains the lymphatic channel. The channel is identified where it enters the axilla and it is dissected until it enters and stains a first-echelon node.[16] Both techniques are used in combination to obtain the most accurate result.[17]

For pathological examination, each sentinel node is processed separately. If the sentinel node is positive for tumor involvement, an axillary dissection will follow.

Adjuvant systemic therapy

Many women with stage I and II breast cancer require today adjuvant systemic treatment either chemotherapy and/or hormonal therapy. The goal of systemic treatment following primary surgery is to eliminate or delay the subsequent appearance of clinically occult micrometastatic disease.

Chemotherapy for breast cancer is usually a combination of anthracycline-based regimens, for example AC (adriamycine, cyclofosfamide), FAC (fluorouracil, adriamycine and cyclofosfamide) or TAC (taxotere, adriamycine and cyclofosfamide).[6]

Hormonal therapy is based on the presence or absence of the estrogen receptor (ER) and/or progesterone receptor (PR) status of the breast cancer cells. Tamoxifen is the most widely used hormonal therapy in breast cancer and the effectiveness extensively studied and proven.[18] Today are beside tamoxifen the aromatase inhibitors available in breast cancer treatment. Another way of hormonal therapy might be medical ovarian ablation with luteinizing hormone - releasing hormone (LHRH) or surgical ablation (surgical removal of the ovaries). It might be expected that a part of systemic chemotherapy may be due to treatment-induced amenorrhea.

Treatment related morbidity

Breast cancer treatment is from its early beginning associated with upper limb morbidity including pain and numbness, reduced range of motion of the shoulder, muscle weakness of the arm and hand and lymph oedema.[19-21]

Halsted introduced in 1894 the radical mastectomy and was the first author who described upper limb morbidity after treatment of breast cancer.[19] Afterwards in the early seventies (20th century) with the replacement of the radical mastectomy by the modified radical mastectomy there was a marked reduction in the incidence of upper limb morbidity.[20-27] Despite further introduction of less extensive surgical procedures such as breast conserving treatment, consisting of local tumor excision, ALND and adjuvant radiation therapy of the breast, this treatment still resulted in upper limb morbidity in a considerable amount of patients.[9,28-30]

Primarily the surgical treatment of the axilla (ALND) gives rise to long-term problems with shoulder movement and lymph oedema of the arm.[7,9,10,31] Additional radiation therapy of the axilla may increase upper limb morbidity due to late normal tissue radiation injury.[21,30,32-37] In the early nineties (20th century) sentinel lymph node biopsy (SLNB) was introduced for staging of the axilla.[15,38] SLNB is nowadays an

excellent alternative for ALND in patients with clinically negative lymph nodes.[39] Much research has been performed to evaluate SLNB related morbidity in comparison to ALND related morbidity.[40-52] The majority of these studies reported less morbidity for SLNB in comparison to ALND.[41-52] A shortcoming however in most of these studies is the absence of pre-treatment assessment and the absent of reliable and validated assessment instruments.

Activities of Daily Life (ADL) and Quality of Life (QOL) in relation to treatment modalities and treatment related upper limb morbidity was scarcely subject of study in the past. However, there is some evidence that patients with breast conserving therapy have a better outcome concerning body-image and related items in comparison to mastectomy patients.[53-56] Also there is evidence that aspects of upper limb morbidity may interfere with ADL and QOL.[57-63]

Aim of the thesis

The primary aim in this thesis is to study upper limb morbidity, perceived disabilities in ADL and QOL within two years after onset of breast cancer treatment comparing breast cancer patients with SLNB only and breast cancer patients treated with ALND. The main research questions answered in this thesis are:

1. What is known in literature about upper limb morbidity in relation to ADL and QOL after breast cancer treatment?
2. What are the short-term, middle-term and long-term upper limb morbidity and perceived disabilities in ADL after breast cancer treatment?
3. What are the changes in QOL two years after onset of breast cancer treatment?
4. What are the differences between SLNB and ALND concerning upper limb morbidity and perceived disabilities in ADL and QOL?
5. Which treatment variables can predict upper limb morbidity, perceived disabilities in ADL and reduction of QOL?
6. What is the relationship between upper limb morbidity and perceived disabilities in ADL and QOL?

Outline of the thesis

This study was performed as a multicentre study in which the following departments were involved: Department of Rehabilitation Medicine, Surgical Oncology and Radiation Oncology of the University Medical Centre Groningen, the department of Rehabilitation Medicine and Surgery of the Martini Hospital Groningen and the Northern Centre for Health Care Research, University Groningen, The Netherlands.

The *first chapter* describes the introduction and outline of the thesis.

The *second chapter* presents a systematic review we performed to evaluate the results of studies, analyzing late morbidity of breast cancer treatment in relationship with ADL and/or QOL and is also an extensive introduction to the main subject of the thesis.

Chapter 3 describes a retrospective pilot study with assessments including upper limb morbidity, ADL and QOL in patients who underwent a modified radical mastectomy or a segmental mastectomy (breast conserving therapy) with ALND. This chapter discusses also the weak aspects of a retrospective study design and it can be seen as a pilot study in advance of the followed prospective study.

Chapters 4 and 5 focus on short- and middle-term upper-limb morbidity and perceived disabilities in ADL in early stage breast cancer patients comparing SLNB with ALND. It concerns a prospective study with pre-treatment assessments and follow up of 6 weeks (short-term) and one year (middle-term). Correlations between upper-limb morbidity and perceived disabilities in ADL were analysed in chapter 4. Chapter 5 discussed also predictive treatment variables in relation to upper-limb morbidity and perceived disabilities in ADL.

Chapters 6a and 6b focus on phantom breast sensations (PB sensations) and phantom breast pain (PB pain) after mastectomy. Chapter 6a describes a prospective study in which the incidence of PB sensations and PB pain is recorded. Additionally the amount of bothering by PB sensations and PB pain was assessed up till 2 years after mastectomy. Chapter 6b analyses the influence of research methodology on prevalence of PB sensations and PB pain.

In chapter 7 the validity and intra- and interobserver reliability is analyzed of a method of indirect volume measurement. This method utilizes surface measurements and a simplified formula for a frustum to determine limb volumes in patients with breast cancer-related lymph edema of the upper extremity. Volumes were calculated and compared with the water displacement method as a gold standard. This assessment method of arm volume is then used in the study of chapter 8.

Chapter 8 focuses on the prospective studied, two years upper limb morbidity, perceived disabilities in ADL and QOL of 181 patients after breast cancer treatment comparing SLNB with ALND. Also predictive treatment variables in relation to upper-limb morbidity, perceived disabilities in ADL and QOL and correlations between upper-limb morbidity and perceived disabilities in ADL and QOL were analyzed.

A general discussion is presented in *chapter 9* with general conclusions of the performed studies and the clinical relevance and implications of our research. In addition, suggestions are made for future research.

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CHAPTER 2

Late morbidity after treatment of breast cancer in relation to daily activities and quality of life; a systematic review

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Published
European Journal of Surgical Oncology 2003;29(3):229-38.

Abstract

Background
Breast cancer treatment may result in long-term upper limb morbidity: reduced range of motion of the shoulder, muscle weakness of the arm and hand, lymph edema, pain and numbness. Relationship of this late morbidity with activities of daily life (ADL) and quality of life (QOL) is infrequently described and the strength of this relationship is not clear.
Methods
A systematic review was performed to evaluate the results of studies, analyzing late morbidity of breast cancer treatment in relationship with ADL and/or QOL. A literature search over the last 20 years (1980-2000) was performed in the databases MEDLINE, EMBASE, PSYCHLIT and CANCERLIT. Methodological quality of selected articles was assessed and additional, aspects of treatment related late morbidity and the relationship to ADL and/or QOL were summarized.
Results
From the 1642 yielded articles 15 fulfilled our primary selection criteria. Only six articles could be selected due to the inappropriate methodological quality. There was high variation in prevalence of pain (12-51%), impairments in range of motion (2-51%), edema (6-43%) and decreased muscle strength (17-33%). Four articles reported significant relationships between late morbidity of the upper limb and perceived disabilities in ADL/QOL. The strength of these relationships was rather low.
Conclusions
Few studies investigated the relationship between late morbidity of the upper limb after treatment of early breast cancer and ADL/QOL. Significant relationship between late morbidity and restrictions of daily activities and poorer QOL was reported, however, the strength of this relationship was rather low.

Introduction

The incidence of breast cancer in the Netherlands is 100 / 100.000 women per year.[1] One out of nine women will develop breast cancer, of which 79% will survive at least five years.[1-3]

The aim of breast cancer treatment is to obtain maximal locoregional control, optimal lymph node staging with minimal treatment related morbidity, good functional result and when possible preservation of the breast.

Halsted introduced in 1894 the radical mastectomy in the treatment of breast cancer.[4] The radical mastectomy was associated with extensive upper limb morbidity including impairments such as reduced range of motion of the shoulder, muscle weakness of the arm and hand, lymph edema, pain and numbness.[5-8] Fortunately, these impairments have become less common as the radical mastectomy has been replaced by the modified radical mastectomy in which the pectoralis muscles were preserved.[7,9-13] Breast conserving treatment, consisted of local tumor excision and adjuvant radiation treatment of the breast, was introduced for early breast cancer in the sixties and further developed in the seventies and eighties.[14-20] However, these less extensive procedures still resulted in upper limb morbidity in a considerable amount of patients.[21-24]

The axillary lymph node status is the most significant prognostic variable in patients with breast cancer.[25,26] Axillary lymph node dissection is therefore an important diagnostic and treatment procedure.[27] This dissection may also result in long-term upper limb morbidity.[6,8,24,27-31] Recently the sentinel node procedure was introduced to reduce the number of unnecessary axillary lymph node dissections, and thereby reducing treatment morbidity from a complete axillary lymph node dissection.[32-35]

Additional radiation therapy of the axilla may increase upper limb morbidity due to late normal tissue radiation injury.[6,23,30,36-41] The appearance of this type of injury dictated a stepwise reduction in radiation dose and increasing fractionation throughout the sixties.[21,22] Since the early seventies the standard treatment policy of radiation therapy is a moderate doses (50 Gy) to the breast and locoregional lymph drainage area such as axilla and supraclavicular, with higher doses directed only to the tumor bed.[21] Radiation therapy only to the breast did not increase incidence of upper limb morbidity.[28]

The incidence of late morbidity after breast cancer treatment: arm edema and reduced range of motion of the shoulder, varies widely due to differences in study population, surgical procedures, radiation dose and fractionation and assessment methods. Late morbidity may interfere with activities of daily life (ADL) and quality of life (QOL).[42-44] However, it is not clear how strong the relationship is between late morbidity (pain, edema, restriction of range of motion and muscle weakness) and ADL and QOL.

This systematic review was performed to evaluate the results of studies, analyzing late morbidity of breast cancer treatment in relationship with ADL and/or QOL.

Methods

Literature search

The search for relevant publications in the literature over the last 20 years (1980-2000) was performed in the databases MEDLINE, EMBASE, PSYCHLIT and CANCERLIT.

Three sections of mesh headings were used. The first section contained the mesh headings "breast cancer" or "mastectomy". The second section contained "physical examination", "edema", "lymph edema", "paresthesia", "arm", "morbidity" or "ADL". Mesh headings in the third section were "QOL", "follow up", "treatment outcome", "rehabilitation", "disability evaluation", "prospective studies", "functional assessment" or "assessment". Additional words such as "functional", "sensation", "fractionation", "conserving" were searched in the title of the publications. Finally the three sections were connected to each other. No language restriction was applied. The abstracts of publications found were screened and selected by the first author (JR) on the basis of the following criteria:

1. the patients must have early breast cancer, defined as a clinical stage I ($pT_1N_0M_0$) or II ($pT_{1,2,3}N_{0,1}M_0$),
2. the treatment modalities studied, must either be a modified radical mastectomy or breast conserving surgery alone or in combination with radiotherapy and/or chemotherapy,
3. late morbidity of the locomotor system must be studied with an interval of minimal one year after the surgical treatment,
4. the relationship of this late morbidity with ADL and/or factors of QOL must be investigated.

Lastly, the reference list of the selected articles generated by the search and the screening were searched for articles not found by the computer. Excluded were case reports, pilot studies and abstracts.

Critical review

The quality of the selected articles was assessed by using a checklist of 30 items concerning general methodological aspects of the studies and the assessment tools used (Appendix I). The greater part of the checklist (item13-29) was related to the application of measurement instruments and the description of their reliability and validity. Reference articles cited by the authors in relation to reliability and validity of the measurement instruments were retrieved and also assessed according to the same criteria.

The criteria were scored on a dichotomous scale: score "1" if the criterion was met and "0" if the criterion wasn't met. Two reviewers (JG, PD) independently assessed all the selected articles. In a consensus meeting the scores of the two reviewers were compared. As a measure of interobserver agreement Cohen's Kappa was calculated.

When there was disagreement in the assessment score, consensus was reached by means of discussion. In cases of persistent disagreement a third reviewer (JR) gave the final judgment.

In addition to the methodological assessment of the articles (Table 1), aspects of treatment related late morbidity and the relationship of this late morbidity to ADL and/or QOL were summarized (Table 2).

Results

The literature search yielded 2127 articles of which 485 articles were double registered thus 1642 articles remained. From the 1642 articles 15 fulfilled the previous described selection criteria.[30,39,41,43-54] Another 31 reference articles were retrieved necessary for assessment of the methodological criteria.

Cohen's Kappa was 0.88. In all scores a consensus was met. Seven items (items 6,18,20,24,26-28) of the criteria list scored constant. After exclusion of these seven items from the calculation, the Cohen's Kappa was 0.87.

In Table 1 the consensus score for each article is presented. The maximum score that could be obtained was 30. None of the selected articles received the maximum score. The highest score obtained was 13 by Swedborg et al.[43] Six out of the 15 articles reached a score of one-third (10) of the maximum score. The general methodological aspect of the studies (items 1-11 and 30) scored moderate within these articles. In 14 articles there was a clear description of inclusion criteria. However, exclusion criteria were only mentioned in four articles. In most studies the study design was prospective or at least longitudinal. Only two studies accomplished the criteria of a randomized control study. In nine of the studies a stratified analysis was applied. The extent of the surgical procedure was more frequently described (10 times) as compared to the extent and dose of the radiation therapy (seven times). Adjunctive treatments such as chemotherapy or hormonal therapy were reported in seven articles. Eleven articles reported the number of dropouts. In two studies a pretreatment baseline assessment was performed.[41,50] All articles described the measurement instruments used (items 12-17). Most frequently these instruments assessed pain, lymph edema or functional performance (items 13, 15 and 16). In only five articles, instruments to assess range of motion or strength were used. The items reliability and validity of the measurement instruments (items 18-29) scored poorly. Six articles fulfilled some of these items. Out of the measurement instruments, reliability of QOL questionnaire had the highest score with a positive assessment within four articles.

As mentioned, six articles fulfilled ten or more of the methodological criteria (Swedborg et al, 1981[43], Segerström et al, 1991[46], Maunsell et al, 1992[49], Tasmuth et al, 1996[50], Sugden et al, 1998[41], Hack et al, 1999[54]) and these articles will be discussed in more detail (Table 2).

The surgical treatment modalities described in these six articles were modified radical mastectomy or breast conserving treatment both with axillary clearance. Only in the article of Maunsell et al, 1992 it was reported that 7% of the patients had no axillary clearance.[49] In the two earliest articles, only modified radical mastectomy with axillary clearance was applied.[43,46] In the two most recent studies two-third of the patients had a breast conserving treatment.[41,54] Radiation therapy was applied in all studies on chest wall or breast covering the parasternal and supraclavicular nodes and adjuvant at the axillary nodes in four of the studies.[41,43,46,50] In one article the radiation therapy was not specified.[49]

Late morbidity

Pain

All six studies assessed the incidence of pain. The assessment instruments varied from self-constructed questionnaires, subjective rating scales and VAS scores to validated pain questionnaires. One study used three different instruments to assess pain.[54] The prevalence of pain one year or later after treatment of breast cancer ranged from 12% to 51% between the studies. No significant relationship was found between pain perception and the type of breast surgery (conservative or amputation) and radiation therapy.[41,50,54] One author found a significant relationship between pain, age, number of axillary nodes dissected and chemotherapy.[54] Factors increasing pain were sleeping on the operated side, reaching out, carrying, working with the arm, housework and handicraft.[50]

It was found that the incidence of pain increased from 23% to 39% in the follow up from 14 to 38 months after treatment.[46] However, others found a decrease in the incidence of pain 6 to 12 month after treatment[50] or did not found a relationship to the time elapsed since the treatment.[54] Thus no clear relationship between pain and follow up period after treatment can be deduced from the reviewed articles.

Range of Motion

The assessment of the range of motion of the arm was performed by physical examination[43,46,50,41,54] or a subjective rating by the patient.[49] A goniometer was used only in one article.[41] Maunsell et al. assessed the range of motion by letting choose the patient from five images representing the capacity to lift the arm through a 180° range.[49] Abduction of the shoulder was assessed in all studies.

The prevalence of restricted range of motion of the affected arm varied from 2%, to 51% of the patients. A severe reduction of the range of motion (more than 50% reduction) was found in 2% of the patients.[43] The mobility of the shoulder was significantly less for the patients receiving radiotherapy on the axilla.[41,43] Range of motion was significantly smaller in the patients with mastectomy as compared with patients with a breast conserving treatment.[41]

Table 1. Methodological assessment scores of the selected Studies

Study		Swedborg 1981 [43]	Aitken 1989 [39]	Bentzen 1989 [30]	Hamilton 1990 [45]	Segerström 1991 [46]	Ivens 1992 [48]	Maunsell 1992 [49]	Sneeuw 1992 [47]	Tobin 1993 [44]	Tasmuth 1996 [50]	Carpenter 1998 [51]	Warmuth 1998 [52]	Sugden 1998 [41]	Velanovic 1999 [53]	Hack 1999 [54]	total
study population	1	1	1	-	1	1	1	1	1	1	1	1	1	1	1	1	14
	2	1	-	1	-	-	-	1	-	-	-	1	-	-	-	-	4
study design	3	-	-	-	-	1	-	1	-	-	1	-	-	1	1	-	5
	4	-	-	-	-	1	-	1	-	-	1	-	-	1	-	-	4
	5	1	1	-	-	-	-	-	-	-	-	-	-	-	-	-	2
allocation procedure	6	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0
	7	1	1	1	-	-	-	1	-	1	-	-	1	1	1	1	9
treatment description	8	1	1	1	1	1	-	-	1	-	1	-	1	1	-	1	10
	9	1	1	1	1	1	-	-	1	-	-	-	-	1	-	-	7
dropouts	10	1	-	-	1	1	-	1	1	1	1	1	1	1	-	1	11
baseline measurement	11	-	-	-	-	-	-	-	-	-	1	-	-	1	-	-	2
measurement instruments	12	-	1	-	-	-	1	1	-	-	-	-	1	1	-	-	5
	13	1	-	1	1	1	1	1	-	-	1	1	1	-	-	1	10
	14	1	1	-	-	-	1	-	-	-	1	1	-	-	-	-	5
	15	1	1	1	-	1	1	-	1	1	1	1	1	1	1	-	12
	16	1	1	1	-	1	1	1	1	1	1	-	1	1	-	1	12
	17	1	-	-	-	-	-	1	1	1	1	1	-	-	1	1	8
reliability	18	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0
	19	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1
	20	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0
	21	1	-	-	-	1	-	-	-	-	-	-	-	-	-	-	2
	22	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	1
	23	-	-	-	-	-	-	1	1	1	-	-	-	-	-	1	4
validity	24	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0
	25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1
	26	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0
	27	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0
	28	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0
	29	-	-	-	-	-	-	-	-	1	-	-	-	-	-	1	2
confounding aspects	30	-	-	1	1	-	-	-	-	-	1	1	1	1	-	1	7
total		13	9	8	6	10	6	11	9	8	12	8	9	12	5	12	

Abbreviations: the assessment items 1-30 are fully described in appendix 1.

Table 2. Breast cancer treatment modalities, late morbidity in relation to ADL/QOL

Reference	sample size (n) dropout rate (n/%)	treatment (%)					late morbidity	(%)	assessment method and follow up	relationship late morbidity with ADL/ QOL	
		BCT	MRM	RT+ CWBR	RT+ N	RT-					
Swedborg et al. 1981 [43]	475	0	100	70	70(#)	30	(#)		phys exam	disabilities:	% of patients
							pain	18	VOL/ROM/grip strength	ADL	9%
							ROM (abduction)	51	subjective rating	household chores	50%
							edema	15	discomfort/pain/ADL difficulties	appearance	19%
							grip strength	33	49 M post surgery	clothes	13%
Segerström et al. 1991 [46]	100 7 (7%)	0	100	100	57	0	pain	39	phys exam: VOL/ROM	edema - FI	(p<0.01)
							ROM	49	questionnaire	ROM- FI	(p<0.01)
							edema	43	pain / FI		
							FI	63	38 M post RT		
Maunsell et al. 1992 [49]	223 22 (13%)	35	65	?	?	?	pain	51	interview	nr. arm problems and	
							numbness	49	questionnaire	psychological distress	(p<0.001)
							ROM	16	PSI		
							edema	24	18 M post surgery		
							strength	18			
Tasmuth et al. 1996 [50]	105 12 (11%)	43	57	63	24	37	pain (breast)	23	phys exam	pain - ADL	(p<0.01)
							pain (arm)	17	ROM/grip strength		
							numbness	80	questionnaire	chronic symptoms and	
							edema	38	VAS (pain), STAI/depression	anxiety/depression	(p<0.01)
							grip strength	17	12 M post surgery		
							phantom sensation	25			
Sugden et al. 1998 [41]	141 14 (10%)	72	28	100	35	0	pain	12	interview	treatment and ADL disabilities:	
							numbness	51	phys exam	MRM>BCT (dressing)	
							ROM	48	functional assessment		
							edema: subj	29	18 M post RT		
							obj	6			
Hack et al. 1999 [54]	248 26 (11%)	64	36	61	0	39	state pain	31	phys exam: ROM		% of patients
							pain/ROM	73	questionnaire	pain related disability	57%
							numbness	63	Pain: MPPQ/SF-MPQ/PDI		
							strength	18	EORTC QLQ-C30/MHI	pain and QOL	(p<0.001)
									33 ± 23 M post surgery	pain and MH	(p<0.01)

Abbreviations: BCT = breast conservative treatment; MRM = modified radical mastectomy; RT+ = radiation therapy; RT- = no radiation therapy; CWBR = chest wall/breast; N = axillary nodes; ADL = activities of daily living; QOL = quality of life; phys exam = physical examination; subj = subjective; obj = objective; VOL = volume; ROM = range of motion; M = month; FI = functional impairment; PSI = psychiatric symptom index; nr = number; STAI = state and trait anxiety; MPPQ = modified post-operative pain questionnaire; SF-MPQ = short-form McGill pain questionnaire; PDI = pain disability index; EORTC QLQ-C30 = The European Organization for research and Treatment of Cancer Quality of Life Questionnaire; MHI = mental health inventory; MH = mental health; # These data were abstracted from an article referred to (Swedborg et al. 1981).38

Edema

Swelling of the affected arm was assessed in five studies. Different methods were used. Two studies used the "water displacement method"[43,46], two studies used the circumference method[41,50] and one[49] used a questionnaire to assess perceived problems as a result of edema. Different criteria for edema were used. Edema of the arm was defined as a volume difference between the arms of more than 10% [43] or 150 ml [46], an increase of the circumference of the affected arm on two sites of at least 2 cm compared to the preoperative circumference [50] or a relative arm circumference value of more than 110% compared to the contralateral arm.[41]

The prevalence of arm edema varied from 6% to 43%. Patients with mastectomy had significantly more frequently edema as compared to patients with breast conserving treatment.[41,50] Edema of the arm correlated significantly with axillary lymph node dissection and receiving radiotherapy.[43,49]

Strength

Muscle strength of the arm at the treated side of the patients was assessed in four studies. The assessment method varied from physical assessment of grip strength [43,50] to subjective reported weakness.[49,54] The prevalence of strength reduction ranged between 17% and 33%. The decrease in grip strength is significantly greater if the dominant side had been operated as compared with the non-dominant side.[50]

Activities of daily life and quality of life

All studies assessed although in different ways the relationship between the late morbidity and ADL and QOL. The assessment instruments used, varied from self-constructed questionnaires, subjective rating scales concerning performed ADL to reliable and valid questionnaires (Table 2). None of the six selected articles described valid or reliable instruments for assessment of ADL. Only one author used a reliable and validated instrument; the pain disability index (PDI) to assess pain related disabilities.[54] Four studies assessed some aspects of QOL, but only one study used a valid and reliable instrument; the European organization for research and treatment of cancer quality of life questionnaire (EORTC QLQ-C30).[54]

Relationship of late morbidity to ADL

A significant relationship was reported between edema and restricted range of motion and patients own assessment of functional impairments.[46] Although 9% of the patients showed some restriction in daily life activities through edema, 50% reported interference of their swollen arm with household chores.[43] One author used a scale, which contained ten functions of daily independent living to assess functional ability.[41] Patients with a mastectomy reported more problems as compared to patients with a breast-conserving treatment. Functions of ADL giving difficulties for both groups were: pulling sweater over head (20%), fasten bra (18%), doing up back zipper (72%), reaching over head (16%) and carrying heavy bags (29%).[41] ADL such as sleeping on

the operated side, reaching out, working with the ipsilateral arm, housework or handicraft are significantly correlated with perceived aggravation of chronic post-treatment pain intensity.[50]

Relationship of late morbidity to quality of life

The number of perceived arm problems 18 month after treatment of breast cancer was significantly associated with high psychological distress assessed in Psychiatric Symptom Index.[49] Compared with women reporting no problems in the affected arm due to late morbidity, the adjusted odds ratios for having substantial psychological distress in women reporting one or two, three or four and five to six arm problems were 1.9, 4.4 and 6.1 respectively (X^2 for trend = 14.0, p = 0.0002).[49] Women who had axillary dissection reported significantly more arm problems due to late morbidity.

The number of symptoms reported preoperatively and the number of chronic symptoms of late morbidity in the operated side correlated significantly with the level of anxiety and depression.[50] One author investigated the physical and psychological morbidity after axillary lymph node dissection using the EORTC QLQ-C30.[54] Overall, just about half of the patients experienced pain-related discomfort and disability. The QOL and mental health of the patients were generally good. Regression analysis showed a significantly negative association between patients subjective reports of pain and the QOL. The disabling impact of their pain on self-care, sexual activities and general arm motion predicted a poorer mental health.[54]

Discussion

In the last twenty years only a few studies investigated the relationship between late morbidity of the upper limb one year or later after treatment of early breast cancer and the perceived disabilities and/or QOL.[30,39,41,43-54] A systematic literature search revealed 15 articles out of 1642 articles. The methodological quality of these15 articles was poor. Only 6 of the 15 articles fulfilled one third of our criteria. The checklist applied in this review consisted of two parts, one concerning general methodological aspects of studies and one concerned assessment instruments and their reliability and validity. If we skipped the criteria covering reliability and validity of applied assessment instruments and used the same relative cut off point, 14 articles would be included. However, we set a high standard and justify this choice as follows: if a relation between impairments and disability and/or QOL is found, it must be clear that these conclusions depend on outcomes of reliable and valid assessment instruments.

Because of the differences in the assessment techniques used for the impairments as well for the disabilities and/or QOL and because of the poor methodology, no meta analysis could be performed.

To analyze the interobserver agreement, all the selected articles were assessed by two reviewers independently. After exclusion of seven items of the methodological checklist which scored constant and thus may give an artificial high overall Cohen's Kappa, the measure of agreement remained high (Overall Cohen's Kappa: 0.87).

Only two studies, Swedborg et al. and Aitken et al. described the design of a randomized clinical trial.[39,43] However, in relation to the topic of this systematic review the type of study design is of less importance. Surprisingly only two studies applied a pretreatment baseline measurement.[41,50] In our opinion this baseline measurement is of considerable importance to assess a point of departure by which the later measurements can be compared.

Assessment of late morbidity

As mentioned earlier a great variability in the applied assessment instruments for impairments was found. In addition, no uniform criteria exist for impairments in pain, range of motion, volume or muscle strength. This lack of criteria may partly explain the variation in prevalence of pain (12-51%), impairment of range of motion (2-51%), edema (6-43%) and decreased strength (17-33%).[41,43,46,49,50,54] The different treatment modalities in the selected studies may also attribute to the variation in prevalence of impairments, as was found by Sugden et al. who reported that patients with a mastectomy had significant more restrictions in range of motion and edema compared to patients with a wide local excision.[41]

Assessment of ADL and/or QOL

Also a wide variability in assessment instruments for ADL was found. The lack of uniformity and reliability/validity of these instruments weakened the validity of the results of the different studies. Additionally comparison of the results is very difficult. Only four articles assessed some aspects of QOL.[43,49,50,54] It seems that QOL is valued poorly in studies concerning the treatment for early breast cancer. However this impression may be the result of our selection criteria.

Late morbidity (impairments) in relation to ADL and/or QOL

The 6 articles reviewed, reported relationship between to the treatment of early breast cancer related impairments of the upper limb and perceived disabilities and/or QOL. Although the reported relationships were significant in four of the articles, the clinical relevance of this relationship is not clear.

The data of Segerström et al. show a rather low relative risk between the presence of edema of the arm and the assessment of functional impairments (RR = 1.6).[46] The same RR (1.6) can be calculated for the presence of restricted range of motion and estimated functional impairments.[46] However, detailed description of these functional impairments is not given.

A more detailed description of perceived problems of several ADL was given by Sugden et al.[41] The significant difference in prevalence of late morbidity between the two treatment groups (mastectomy and wide local excision) was also reflected in these perceived problems of ADL. But the author did not provide the strength of the relationship between late morbidity and perceived problems of ADL.

An inverse relationship between the performance of ADL and aggravating pain was reported by Tasmuth et al.[50] Although a significant relationship was reported, the strength of the relationship was not described.

Other results were reported by Maunsell et al. who found a strong relationship between the reported number of perceived arm problems and a high Psychiatric symptom index.[49] The adjusted odds ratios for having substantial psychological distress in women reporting one or two, three or four and five to six arm problems were 1.9, 4.4 and 6.1 respectively (X^2 trend = 14.0).

Hack et al. reported a relationship between subjective reported pain and QOL but also in this study the explained variance was weak (r^2 = 14%).[54] Late morbidity was associated with axillary lymph node dissection and with axillary radiation therapy.[41,43,49,54] These results may indicate an association between axillary lymph node dissection and/or axillary radiation therapy with poorer QOL. But the strength of this association is unclear.

Conclusion

In the last twenty years (1980-1999) only a few studies investigated the relationship between late morbidity of the upper limb one year or later after treatment of early breast cancer and the perceived disabilities and/or QOL. The overall methodological quality of these articles was limited. Little attention was paid to reliability and validity of the assessment tools. Six articles fulfilled one third of the estimated methodological criteria.

These six articles described significant relationship between late morbidity after treatment of early breast cancer and restrictions of daily activities and poorer QOL. However, the strength of this relationship is overall low or not given. Clinical relevance of the relationship is up till now poorly investigated.

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Appendix 1

Criteria list for the assessment of the ***methodological quality*** of the selected studies.

Study population

1. The study received 1 point if there is a clear description of inclusion criteria.
2. The study received 1 point if exclusion criteria were described.

Study design

3. The study received 1 point if the design is longitudinal.
4. The study received 1 point if the design is prospective.
5. The study received 1 point if it is a randomized control study.

Allocation procedure

When it is a randomized control study; the randomization procedure is adequate.

6. The study received 1 point if concealed allocation and random sequence generation is applied.

When it is a cohort study; the matching procedure is adequate.

7. The study received 1 point if the treatment groups are comparable according to two following criteria; age and the pretreatment morbidity status or a stratified analysis is applied.

Description of the treatments

8. The study received 1 point if there is a clearly description of the extent of surgical procedure in the various groups.
9. The study received 1 point if there is a clearly description of the daily radiation dose and localization.

Dropouts' description

10. The study received 1 point if the number of dropouts is described.

Measurement

11. The study received 1 point if a pretreatment baseline measurement is performed.

Measurement instruments

12. The study received 1 point if a measurement instrument to assess the range of motion of the shoulder joint was used.
13. The study received 1 point if a measurement instrument to assess perceived pain was used.
14. The study received 1 point if a measurement instrument to assess strength of the upper limb was used.
15. The study received 1 point if for using a measurement instrument to assess lymph edema of the upper limb was used.
16. The study received 1 point if a measurement instrument to assess the functional performance/ perceived disabilities was used.
17. The study received 1 point if a measurement instrument to assess the quality of life was used.

Reliability

18. The study received 1 point if reliability of instrument(s) measuring range of motion, has been reported by the authors or has been established in studies cited by the authors.
19. The study received 1 point if reliability of instrument(s) measuring perceived pain, has been reported by the authors or has been established in studies cited by the authors.
20. The study received 1 point if reliability of instrument(s) measuring strength has been reported by the authors or has been established in studies cited by the authors.
21. The study received 1 point if reliability of instrument(s) measuring lymph edema of the arm has been reported by the authors or has been established in studies cited by the authors.
22. The study received 1 point if reliability of instrument(s) measuring functional performance/perceived disabilities has been reported by the authors or has been established in studies cited by the authors.
23. The study received 1 point if reliability of instrument(s) measuring quality of life has been reported by the authors or has been established in studies cited by the authors.

Validity

24. The study received 1 point if validity of instrument(s) measuring range of motion, has been reported by the authors or has been established in studies cited by the authors.
25. The study received 1 point if validity of instrument(s) measuring perceived pain, has been reported by the authors or has been established in studies cited by the authors.
26. The study received 1 point if validity of instrument(s) measuring strength, has been reported by the authors or has been established in studies cited by the authors.
27. The study received 1 point if validity of instrument(s) measuring lymph edema of the arm, has been reported by the authors or has been established in studies cited by the authors.
28. The study received 1 point if validity of instrument(s) measuring functional performance/perceived disabilities, has been reported by the authors or has been established in studies cited by the authors.
29. The study received 1 point if validity of instrument(s) measuring quality of life, has been reported by the authors or has been established in studies cited by the authors.

Confounding aspects

30. The study received 1 point if adjunctive treatments are reported.

CHAPTER 3

Impairments, disabilities and health related quality of life after treatment for breast cancer; A follow-up study 2.7 years after surgery

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Published
Disability and Rehabilitation 2004;26(2):78-84.

Abstract

Purpose
The aim of this study was to assess impairments, disabilities and health related Quality of Life (QOL) after treatment of breast cancer and to analyze the relationship between treatment modalities, impairments, disabilities and health related QOL.
Method
Fifty-five patients who underwent a modified radical mastectomy or a segmental mastectomy with axillary lymph node dissection were retrospectively assessed with a mean follow up of 2.7 years after treatment. Impairments were assessed by means of measuring active shoulder range of motion, grip strength, arm volume and pain. Disabilities were assessed by means of the Shoulder Disability Questionnaire (SDQ) and health related QOL was assessed by means of the RAND 36-item Health Survey (RAND-36). Setting: University Hospital Groningen, The Netherlands.
Results
Pain (60%) and reduction of grip-strength (40%) were the most frequent impairments found. The prevalence of impaired range of motion and edema was 9-16% respectively 15%. Mean group score of the SDQ was 33.7 (sd 32.1) and mean scores of the RAND-36 differed significantly for physical functioning, vitality and health perception to that of a female norm group. Radiotherapy and chemotherapy were significant factors in the prediction of impaired range of motion. Pain and restricted range of motion explained 61% respectively12% of the variance in disability (SDQ). In the prediction of health related QOL, pain, grip strength and arm volume were significant factors respectively in six, three and two domains.
Conclusions
Pain is the most frequent assessed impairment after breast cancer treatment with strong relationship to perceived disability and health related QOL. Disability is mild and health related QOL (RAND-36) differed in three of the nine domains with a female norm group.

Introduction

The incidence of breast cancer is in the Netherlands 127 / 100.000 women per year.[1] One out of nine women will develop breast cancer, of which 79% will survive at least five years.[1-3]

Contemporary treatment options are breast conserving surgery or modified radical mastectomy followed by adjuvant locoregional radiation and/or systemic treatment with chemotherapeutic or hormonal agents. These treatment options may in itself induce impairments of the locomotor system. Most common impairments described after treatments of breast cancer are:

reduced range of motion of the shoulder[4-15];
numbness of the axilla or lateral chest wall[16];
reduced grip strength [11,13,14,17,18];
increase in arm volume[5,6,9-13,19-26];
pain.[10,13,14]

Because of the modern treatment options the number of patients cured after breast cancer increases, as do the 5 and 10 year survival.[2,3] As a result, impairments induced by the treatment of breast cancer are becoming more important. If impairments of the locomotor system persist, they may influence the abilities to perform activities of daily living and they may influence the quality of life (QOL) of patients.[5,10-14,18,27,28] QOL is a multidimensional term, which is generally used as a health description. It consists of different domains such as 'physical functioning' and 'social functioning' and 'psychological well being'.[29]

Relationships between impairments, disabilities and QOL in breast cancer patients are scarcely investigated.[29-31] As a consequence a clear picture of the impairments and their influence on disabilities and QOL after breast cancer treatment cannot be acquired from literature, although breast cancer is one of the greatest dangers of health in Western Europe and America.[16,31]

The **aims** of the present study were to:

assess impairments, disability and health related Quality of Life after treatment of breast cancer;
analyze the relationship between treatment modalities and impairments;
analyze the relationship between impairments and disabilities and health related QOL corrected for age.

Patients and methods

All patients who underwent between 1993 and 1995 a modified radical mastectomy or a segmental mastectomy with axillary lymph node dissection in the University Hospital Groningen were included in this study. Of 156 patients the medical records were retrieved. Excluded from the study were patients who underwent mastectomy on both sides, patients with metastases and/or recurrence. In total 111 patients were invited by letter to participate in this study of which 59 patients gave a positive reaction, 27 patients gave a negative reaction and 25 patients did not respond. With four patients no agreement could be reached about an appointment within the available time-span.

Eventually 55 patients were examined for this study. From the records of these patients the following information was extracted: type and side of surgery, adjuvant therapy (chemotherapy, radiotherapy), number of lymph nodes (total number and number of positive nodes) dissected, length of hospital stay (in days), demographic information, and exercise compliance.

Impairments were assessed as follows:

Active shoulder range of motion (forward flexion and abduction) was assessed using a two-armed goniometer. An inclinometer was used to assess passive external rotation[5]; a difference in range of motion between affected side and non-affected side of ≥20° was considered as an impaired range of motion;[32]
Grip strength (cylinder grip) was assessed using a Citec® hand-dynamometer: difference in grip strength between affected side and non-affected side ≥ 10% was considered as an impaired grip strength;[17]
Arm volume was assessed by means of the formula of Sitzia (et al. 1995).[33,34] A difference between affected side and non-affected side ≥ 10% was considered as lymph edema;
Pain was assessed using visual analogue scale (VAS) ;[17] pain was defined as a score on the VAS > 0.

Disability was assessed by means of:

The Shoulder Disability Questionnaire (SDQ);[35-37] the SDQ assesses the hindrance of the shoulder during 16 activities of daily life in which shoulder function is required. The scoring range is 0-100. A higher score indicates a more severe disability.

Health related QOL was assessed by means of the RAND 36-item Health Survey (RAND-36).[38,39] The RAND-36 consists of 36 questions and is a short version of the "RAND Health Insurance Study Questionnaire". It is similar to the MOS SF-36.[40]
The RAND-36 consists of nine domains; physical functioning, social functioning, role limitations, (physically), role limitations (emotionally), mental health, vitality, pain,

general health perception and general health change. A higher score indicates a better well being.

The medical ethical committee of the University Hospital of Groningen approved this study. Statistics included: descriptive statistics, comparison between affected and non-affected side (paired t-test), Spearman's r and regression analyses. In all regression analyses, stepwise forward, age was entered as a correcting factor. The significance level was chosen as α=0.05.

Table 1. Tumor staging and treatment characteristics (n=55)

		n	%
Stage of tumor			
0	(Tis, N0, M0)	2	3.7
I	(T1, N0, M0)	26	47.1
IIa	(T0-2, N1,0, M0)	19	34.5
IIb	(T2,3, N1,0, M0)	8	14.5
Type of surgery			
Modified radical mastectomy		40	72.7
Local excision		15	27.2
Side of surgery			
Dominant		32	58.1
Non-dominant		23	41.9
Number of axillary nodes dissected			
10		22	40.0
11 20		26	47.2
>20		7	12.7
Number of positive nodes			
≤4		49	90.7
>4		6	9.3
Type of adjuvant therapy			
No		27	49.1
Radiation therapy		17	30.9
Chemotherapy		4	7.3
Radiation and chemotherapy		7	12.7
Physical therapy			
No		19	34.5
Yes		36	65.5

Abbreviations: T: tumor; N: node; M: metastasis

Results

Descriptive

The mean age of the patients was 56.7 years (sd 13.3), mean weight was 73.9 kg (sd 16.7). The tumor staging and treatment characteristics are summarized in Table 1. The mean follow-up was 2.7 years (sd 0.7).

Differences between affected and non-affected side and the number of subjects with impairments are summarized in Table 2. The mean group score of the SDQ was 33.7 (sd 32.1). The scores of the RAND-36 are summarized in Table 3. The mean scores of the RAND-36 differed significantly for physical functioning, vitality and health perception to that of a female norm group (n= 691).[38]

Prediction

Predictions of impairments by means of treatment characteristics are summarized in Table 4. In the prediction of disability by impairments explained pain, forward flexion, external rotation and age, 73% of the variance in the SDQ (Table 5). In the prediction of health related QOL (RAND-36) by impairments, pain, grip strength and arm volume were significant factors in 6, 3 and 2 domains of the RAND-36 respectively (Table 6).

Table 2. Physical assessment of affected side and non-affected side and prevalence of patients with impairments at 2.7 (sd 0.7) years follow up after breast cancer treatment (n=55)

	As		Nas			Patients with impairments:	
Physical assessment	mean	sd	mean	sd	p	n	%
Shoulder mobility (°)							
Forward flexion	153.2	26.2	158.9	23.1	.004	5	9
Abduction	156.6	30.1	164.1	19.4	.006	9	16
External rotation	57.3	14.6	63.5	12.6	<.001	6	11
Grip strength (N)	171.6	64.2	183.9	73.4	.135	22	40
Arm volume (ml)	2540.3	710.5	2416.2	610.4	<.001	8	15
Pain (VAS)	2.5	2.7				33	60

Abbreviations: sd: standard deviation; As: affected side; Nas: non-affected side.

Impairments: A difference in range of motion between affected side and non-affected side of ≥ 20° was determined as impaired range of motion.[32] A difference in grip strength between affected side and non-affected side ≥ 10% was determined as impaired grip strength.[17] A difference in arm volume between affected side and non-affected side ≥ 10% was determined as lymph edema. Pain was assessed using visual analogue scale (VAS); pain was determined as a score on the VAS >0.0[17]

Table 3. Group means of the scores of the RAND-36 of the study group at follow up of 2.7 (sd 0.7) years compared with a norm group of 691 females

	Norm group[38] (n=691)		Study group (n=55)				
RAND-36	mean	SD	mean	SD	difference	95% CI	p
Physical functioning	80.7	23.6	72.5	24.2	8.2	1.7 to 14.7	*
Social functioning	86.1	20.9	83.2	19.9	2.9	-2.8 to 8.6	
Role limitations physical	78.3	36.5	69.9	41.9	8.4	-1.7 to 18.5	
Role limitations emotional	82.5	33.5	73.3	41.8	9.2	-0.2 to 18.6	
Mental health	75.5	18.9	70.8	16.6	4.7	-0.4 to 9.8	
Vitality	66.3	19.6	58.2	20.3	8.1	2.7 to 13.5	*
Pain	80.0	25.4	81.2	20.8	-1.2	-8.1 to 5.7	
Health perception	71.5	21.8	64.2	21.3	7.3	1.3 to 13.3	*
Health change	53.4	19.6	53.6	25.6	-0.2	-5.7 to 5.3	

Abbreviations: *; Significant difference ($p<0.05$) between the norm group and the study group; SD: standard deviation; 95% CI means 95% confidence interval.

Table 4. Prediction of impairments by means of treatment characteristics

Dependent	Predictor	β	95% CI of β	r^2 change	r^2 tot
Impairments:					
Forward flexion	Age	-1.1	-1.6 to -0.6	0.26	
	Radiotherapy	-14.7	-27.1 to -2.2	0.08	
	Constant	221.7	192.4 to 250.9		0.34
Abduction	Age	-1.1	-1.7 to -0.5	0.18	
	Radiotherapy	-20.9	-35.5 to -6.3	0.12	
	Constant	226.1	191.8 to 260.5		0.30
External rotation	Age	-0.3	-0.6 to 0.5	0.03	
	Chemotherapy	-10.2	-20.3 to -0.2	0.08	
	Constant	73.9	55.1 to 92.6		0.11

Only significant predictors are represented in the table. The greater the coefficient ß, the greater is the contribution of the independent variable to the explanation of the dependent variable. The r^2-change is a measure for the explained variance of the dependent variable by the independent variables. One hundred percent times r^2-change gives the percentage of explained variance.

Table 5. Prediction of disability by means of impairments

Dependent	Predictor	β	95% CI of β	r^2 change	r^2 tot
Disability: SDQ					
	Age	-0.7	-1.1 to -0.2	0.004	
	Pain in the shoulder	7.7	5.5 to 9.8	0.61	
	Forward flexion	-0.3	-0.6 to -0.1	0.09	
	External rotation	-0.5	-0.9 to -.02	0.03	
	Constant	131.4	75.7 to 187.1		0.734

Only significant predictors are represented in the table.

Table 6. Prediction of health related QOL (RAND-36) by impairments

Dependent	Predictor	β	95% CI of β	r^2 change	r^2 tot
Health related QOL (RAND-36)					
Physical functioning	Age	-0.4	-0.8 to 0.09	0.24	
	Forward flexion	0.3	0.04 to 0.5	0.17	
	Grip strength	0.1	0.03 to 0.2	0.06	0.52
	Arm volume	$-7.7*E^{-7}$	$-0.2*E^{-3}$ to $-0.3*E^{-5}$	0.05	
	Constant	48.6	-9.6 to 106.9		
Social functioning	Age	-0.154	-0.6 to 0.3	0.03	
	Pain in the shoulder	-2.9	-5.0 to -0.8	0.14	
	Constant	98.9	75.3 to 122.4		0.17
Role limitation physical	Age	0.8	-0.01 to 1.6	0.001	
	Grip strength	0.3	0.2 to 0.5	0.20	
	Arm volume	$-2.2*E^{-4}$	$-0.4*E^{-3}$ to $-0.8*E^{-5}$	0.13	0.33
	Constant	19.0	-49.7 to 87.8		
Role limitation emotional	Age	-0.3	-1.2 to 0.6	0.05	
	Grip strength	0.2	0.05 to 0.4	0.11	
	Constant	49.6	-20.4 to 119.6		0.16
Mental health	Age	$1.6*E^{-2}$	-0.3 to 0.4	0.004	
	Pain in the shoulder	-2.3	-4.1 to -0.5	0.12	
	Constant	75.8	55.5 to 96.0		0.12
Vitality	Age	0.1	-0.3 to 0.5	$0.1\ E^{-3}$	
	Pain in the shoulder	-3.8	-5.8 to -1.8	0.23	
	Constant	59.2	36.5 to 81.8		0.23
Pain	Age	-0.1	-0.4 to 0.2	0.05	
	Pain in the shoulder	-.55	-7.1 to -3.9	0.48	
	Constant	101.5	83.7 to 119.4		0.53
Health perception	Age	-0.4	-0.8 to -0.04	0.13	
	Pain in the shoulder	-4.5	-6.3 to -2.7	0.29	
	Constant	96.2	76.2 to 117.1		0.42
Health change	Age	-0.6	-1.1 to -0.07	0.13	
	Pain in the shoulder	-3.8	-6.3 to -1.3	0.14	
	Constant	94.8	63.3 to 123.2		0.27

Only significant predictors are represented in the table.

Discussion

Prevalence of impairments

Pain and loss of grip strength are the most frequent impairments found in this study. The prevalence of pain (60%) is high compared to the prevalence in some other studies ranging from 16% to 21%.[9,13,17,41] However, other studies reported also high prevalence of pain (51 and 73%).[14,18] The high prevalence is partially due to our definition of pain: a score on the VAS > 0. The mean score of pain was low on the VAS (2.5).

Although there is no significant difference between affected and non-affected side, the prevalence of impaired grip strength was 40 % (table 2). In other studies impaired grip strength varied from 16 to 33%.[9,13,14,17,18,41] Although there were significant differences between affected and non-affected side for shoulder range of motion, the prevalence of impaired range of motion (>20°) of the shoulder was low: 9-16%. Different authors have found an impaired range of motion of the shoulder ranging from 2 to 51%, but the cut off points defined by these authors differ considerably making comparison between the results of the studies impossible.[5,9,10,12,18]

The prevalence of arm edema is 15% in our study (Table 2). In other studies prevalence of arm edema varied from 6-43%.[31] The large differences in prevalence of impairments is probably also due to the different assessment methods and definitions of impairments used.[31] For example, edema was assessed with help of the water displacement method,[9,12] the circumference method,[10,13] surface measurements[33] or was based on a patient's self-report.[41] In our study we choose the formula of Sitzia (surface measurements with an interval of 4 cm) because of its proven reliability, its patients friendliness and easy applicableness.[33,34]

Prediction of impairments by treatment modalities

Only radiotherapy and in minor extent chemotherapy were significant factors in the prediction of impaired range of motion (Table 4). Concerning radiotherapy this is in accordance with results from other studies.[7,9,10,41] We found no significant relationship between the number of axillary nodes dissected (extent of axillary dissection) and the assessed impairments, although in other studies with larger number of participated patients, type of surgery and extent of axillary treatment were found to be related to late morbidity.[9,10,18,31]

Relations between impairments, disabilities and health related QOL.

When the impairments are used to predict disabilities, pain explained 61% of the variance in disability score (SDQ) and range of motion (forward flexion and external rotation) explained 12% of the variance in disability score (Table 5). In literature there are very few studies investigating the relationship between late morbidity of the upper limb and the perceived disabilities of breast cancer patients.[31] Also Tasmuth (1996)[13] and Hack (1999)[14] found significant relationship between pain and perceived

disabilities. However they provide no details about the strength of this relationship. Segerström (1991)[12] found rather low relative risks (RR) between the presence of restricted range of motion and the presence of edema of the arm and estimated disabilities (RR = 1.6 for both). As mentioned above also in our study restricted range of motion explained a small part of the variance in disability score. Contrary to the results of Segerström's study the presence of edema of the arm could not predict disabilities related to the shoulder in our study.

When the impairments are used to predict health related QOL, pain was the most important factor in six equations (Table 6), where as grip strength was an important factor in three equations. Looking at the total explained variance (r^2 tot) the influence of impairments upon disabilities is larger than upon health related QOL. This might be explained from the fact that pain and restricted range of motion of the shoulder will interfere more with activities of daily life in which shoulder function is required (SDQ) than with health related QOL. Although the impairments of the arm found in our study correlate significantly with the disability score, they apparently do not result in a high state of disability. This is probably due to the relative mild character of the impairments.

In interpreting the results one must bear in mind the weaknesses of the study. The following considerations are important in this respect:

The response was rather low, probably due to the retrospective character of the study (follow-up almost three-year after treatment). Eventually 55 of the invited 111 patients were assessed. However with a long-term follow-up this was expected. Due to the relative small number of patients studied, the results should be interpreted with caution, as there may be lack of statistical power. In the methods and results section we used the term prediction/predictors as a statistical term. Because of the research design a more appropriate term would be association/associated factor.

The fact that pre-treatment baseline assessment was not performed, also may have introduced some interpretation problems because assessment results of the affected arm now only could be compared with assessment results of the unaffected arm. Introducing clear definitions of the impairments partially solved this problem.

From our results we conclude that impairments described in literature were also found in our population, although in our study they were relative mild. Moderate pain is the most frequently found impairment with strong relationship to perceived disabilities and in lesser extent to health related QOL in patients with breast cancer more than two years after treatment. There is a low degree of disability assessed with the SDQ. The health related QOL assessed with the RAND-36 differed from a female norm population in three (physical functioning, vitality and health perception) of the nine domains.

Implications for Rehabilitation Practitioners are enclosed in the relatively moderate impairments of which pain and reduced range of motion of the shoulder are related to mild disabilities and some factors of health related QOL.

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CHAPTER 4

Short-term morbidity of the upper limb after sentinel lymph node biopsy or axillary lymph node dissection for stage I or II breast cancer

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Based on
Short-term morbidity of the upper limb after sentinel lymph node biopsy or axillary lymph node dissection for stage I or II breast cancer
Cancer 2003;98:690-6. Erratum in *Cancer* 2004;100(9):1991

Abstract

Background
The goals of the sentinel lymph node biopsy (SLNB) are to improving axillary staging and reduce unnecessary axillary lymph node dissections (ALND), thereby reducing treatment related upper limb morbidity. In the current prospective study, short-term upper limb morbidity was assessed after SLNB and/or ALND.
Methods
The study comprised 204 patients with stage I/II breast carcinoma. Mean patient age was 55.6 years (standard deviation, 11.6). Sixty-six patients (32%) underwent SLNB only, and 138 (68%) underwent a level I-II ALND. Assessment (pre-operative [t0] and 6 weeks postoperative [t1]) included evaluation of shoulder range of motion, muscle strength, grip strength, pain, upper/forearm circumference, shoulder disability and activities of daily life (ADL).
Results
Considerable treatment related upper-limb morbidity was observed. Significant ($p<.001$) changes were found for pain, range of motion in forward flexion, abduction and abduction / external rotation, strength of shoulder abductors and elbow flexors and in perceived disabilities in ADL. Also there is significant difference in short-term treatment related morbidity and ADL between SLNB and ALND.
Conclusion
Significant short-term treatment related upper limb morbidity exists after SLNB or ALND. Six weeks after surgery, there is significantly less upper-limb morbidity after SLNB compared to ALND. ALND as well as in lesser extent mastectomy are predictors for short-term upper limb morbidity.

Introduction

The incidence of breast carcinoma in The Netherlands is 127 per 100000 women per year.[1] Of every 10 women, 1 will develop breast carcinoma and 79% will survive at least 5 years.[1,2]

The goals of breast carcinoma treatment are local tumor control, optimal lymph node staging with minimal treatment-related morbidity, good functional results, and breast preservation. Axillary lymph node status is the most significant prognostic variable in patients with breast carcinoma.[3-6] Therefore, axillary lymph node dissection (ALND) is an important diagnostic, staging, and treatment procedure.[7]

However, ALND may result in upper-limb morbidity such as pain, numbness, lymph edema, weakness, and impaired shoulder range of motion.[7-14] Upper-limb morbidity may interfere with the activities of daily life (ADL) and quality of life.[13-21] In the early postoperative period, return to routine activities is usually difficult because of pain and restricted range of motion of the shoulder.[22,23]

The sentinel lymph node procedure was introduced recently to decrease the number of unnecessary ALND's and to reduce surgery related morbidity as a result of ALND.[24-27] Sentinel lymph node biopsy (SLNB) removes selectively the lymph node that receives the metastatic drainage from the tumor. SLNB is an accepted procedure because of its accuracy to predict the presence of metastatic disease in the axillary lymph nodes.[24,25,28,29] Yet, to our knowledge, only a few studies have been performed to evaluate morbidity after SLNB.[26,27,29-35] Follow-up in these studies was less than 2 years and SLNB-related morbidity seemed to be less in comparison to ALND-related morbidity.[26,27,30-35] Although the number of studies investigating upper limb morbidity after breast carcinoma is increasing, the role of SLNB in reducing upper-limb morbidity and perceived disability in all postoperative phases is still not clear.[27,30,32]

The aim of the current study was to analyze prospectively the short-term upper limb morbidity and perceived disability in ADL of patients after SLNB versus ALND.

Materials and methods

From June 1999 to June 2001, patients with Stage I (T1N0M0: tumor 2 cm or less in greatest dimension [T1], no regional lymph node metastasis [N0], no distant metastasis [M0]) or Stage II (T1N1M0, T2N0M0, T2N1M0, T3N0M0: metastasis to movable ipsilateral axillary lymph node [N1], tumor more than 2 cm but not more than 5 cm in greatest dimension [T2], tumor more than 5 cm in greatest dimension [T3]) breast carcinoma participated in a cohort study to assess treatment related upper limb morbidity.[36] Patients were retrieved from two hospitals. The Groningen University Hospital already had been using SLNB in its staging procedure whereas

the Martini Hospital Groningen introduced SLNB halfway during the inclusion period. Informed consent was obtained from the participating patients. The protocol was approved by the institutional review board committees of both institutions.

Data regarding patient characteristics and treatment variables were collected from the medical records. Two groups of patients were distinguished in the current study: patients who underwent SLNB and patients who underwent ALND or ALND after SLNB. Sentinel lymph nodes were identified using both a radioactive tracer and Patent blue dye® (Blue Patenté; Labatoire Guerbet, Aulnay-sous-Bois, France). If metastases were identified in the sentinel lymph node, ALND was performed within 2 weeks after the SLNB. The procedure has been described extensively by Rutgers et al.[37] ALND consisted of a Level I–II axillary dissection. Contemporary surgical treatment included a modified radical mastectomy or breast-conserving treatment.

Upper-limb function and ADL were evaluated 1 day before surgery (t0) and 6 weeks after surgery (t1). Pain was assessed with a visual analog scale (VAS; Table 1). Patients were asked to mark their current pain perception on a 10 cm straight line (0 cm = no pain, 10 cm = worst pain imaginable).[38,39] Upper limb function was assessed during a standardized physical examination (Table 1). Active shoulder range of motion (ROM) was measured with a goniometer (Isomed® inclinometer; Portland, Oregon, USA) according to a standardized protocol in forward flexion, abduction and external rotation (*Figure 1*).[40,41] The muscle strength of the shoulder abductors and elbow flexors was measured using a hand-held dynamometer (Citec®; Groningen, The Netherlands)[42–44] and grip strength was measured with a Yamar® (Bollingbrook, IL) hand-held dynamometer (*Figure 2*).[15,45] All muscle strength measurements were performed three times and the mean of these three measurements was used for further analysis. Upper and forearm circumference was measured with a Gulick Measuring Tape® (Lafayette Instruments; model 258-J00305, Lafayette, Indiana, USA) at 10 cm proximal to the olecranon and 15 cm proximal to the processus styloideus ulnae (*Figure 3*).

ADL was assessed with the Shoulder Disability Questionnaire (SDQ) and the Groningen Activity Restriction Scale (GARS).

The 16-item SDQ is a functional status measure that evaluates the ability of patients with shoulder disorders to perform daily activities.[46,47] The SDQ contains 16 statements that describe the situations in which patients experience pain and what some of the effects may be. It has a three-category response format (e.g., 1: *yes my shoulder is painful when I open or close a door*, 2: *no my shoulder is not painful when I open or close a door*, 3: *I did not perform the activity during the past 24 hours*). The total score for the 16 statements ranges from 0 (no functional status limitation) to 100 (maximum functional status limitation) (Table 1).[46,47]

The GARS assesses the perceived restrictions (disability) in performing 18 ADL tasks.[48,49] It has a four-category response format (e.g.,1: *able to perform the activity without any difficulty*, 2: *able to perform the activity with some difficulty*, 3: *able to*

perform the activity with much difficulty, 4: *unable to perform the activity independently*). The sum score ranges from 18 (the person can perform all the activities without any difficulty) to 72 (the person cannot perform any activity without the help of others; Table 1).[48,49]

Statistical analyses were performed using descriptive statistics and t-tests for independent samples for between-group comparisons and t-tests for dependent samples for within-group comparisons. Pearson Chi-Square test was used for dichotomy variables and Pearson correlations. Also linear regression analysis was performed. Differences were accepted as significant if p values were 0.05 or less.

Table 1. Assessment of Shoulder Function and Activities of Daily Life

Assessment	Assessment tool
Shoulder function:	
Pain (current pain)	Visual Analogue Scale (VAS)[38,39] *(centimeters)*
Numbness	Clinical examination: numbness *yes* or *no*
Active shoulder range of motion:	Isomed® Inclinometer.[40,41] *(degrees)*
Forward flexion	
Abduction	
External rotation	
Combined abduction/external rotation	
Muscle strength:	Citec® handhold dynamometer.[42-44] *(Newton meters)*
Shoulder abductors	
Elbow flexors	
Grip strength (cilinder grip)	Yamar® hand-dynamometer.[15,45] *(Newton meters)*
Upper arm circumference	10 cm proximal to the olecranon
Fore arm circumference	15 cm proximal to the processus styloideus ulnae
	Gulick Measuring Tape (Lafayette Instrument; model 258-J00305) *(centimeters)*
Activities of Daily Life (ADL)	The Shoulder Disability Questionnaire (SDQ)[46,47]
	The Groningen Activity Restriction Scale (GARS)[48,49]

Figure 1. *Active shoulder range of motion (ROM) was measured with a goniometer (Isomed® Inclinometer)*

Figure 2. *Grip strength was measured with a Yamar® hand-held dynamometer*

Figure 3. *Upper and forearm circumference was measured with a Gulick Measuring Tape®*

Results

During 2 years (1999-2001), 204 consecutive patients with invasive breast carcinoma entered the study. Their mean age was 55.6 years (sd, 11.6). Forty-two percent had Stage I (n=85), 42% had Stage IIA (n=86) and 16% had Stage IIb (n=33). Initially 124 (61%) patients underwent a SLNB. Of these patients, 58 (47%) had metastatic disease in the sentinel lymph node(s) and additional ALND was performed. Therefore, the study comprised of 66 patients with SLNB (32%) and 138 patients with a level I-II ALND (68%; *Figure 4*). Of the 66 patients with SLNB, 17 patients received a mastectomy (26 %) and 49 patients received breast-conserving treatment (74%). In the ALND group (n=138), 68 patients received a mastectomy (49%) and 70 patients received breast conserving treatment (51%).

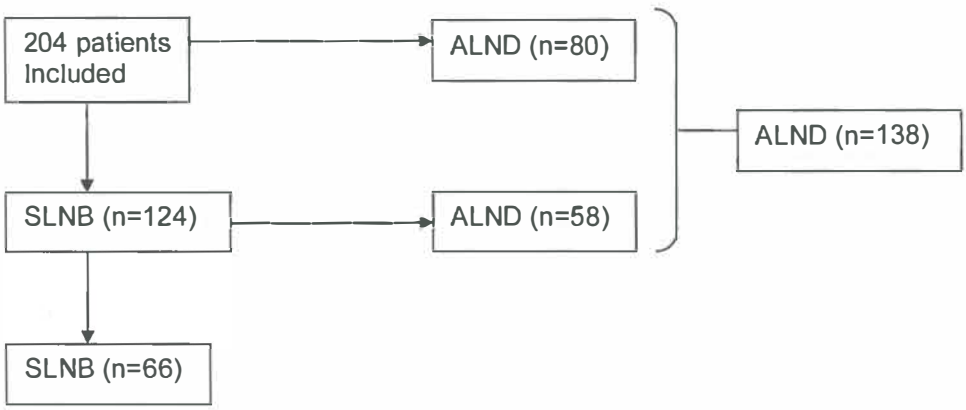

***Figure 4**. Diagram of the included patients.*

***Abbreviations:** SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection.*

Six patients cancelled follow-up appointments before t1; 4 patients belonged to the SLNB group and 2 patients belonged to the ALND group. In the SLNB group one patient refused further treatment and three found the assessment protocol bothersome and chose to withdraw from the study. In the ALND group one patient withdrew from the study due to distant metastases and one because of psychological burden. One hundred ninety-eight patients completed pre- and postoperative assessments, 62 with SLNB and 136 with ALND.

Postoperative complications were scored in both groups. Serome production that lasted longer than four weeks was reported in 3 of 62 patients with SLNB (5%) and 18 of 136 patients with ALND (13 %; p=0.047). Inflammation of the wound that

necessitated antibiotic treatment occurred in 6 of 62 patients with SNLB (10%) and 20 of 136 patients with ALND (15 %), which was not significant (p=0.196).

Significant treatment-related upper-limb morbidity and disability 6 weeks after surgery included pain, decreased ROM in forward flexion, abduction, and abduction/external rotation, and loss of strength of shoulder abductors and elbow flexors (Table 2). The self assessed perception of pain (VAS) increased from 0.4 (sd: 1.2) preoperatively to 1.3 (sd: 2.0) 6 weeks postoperatively (p<.001) (Table 2). One hundred and thirty three patients (67.2 %) perceived postoperative numbness of the axillary region.

The largest decrease in ROM the shoulder was found in abduction (25.5°, sd: 34.2) but there also was a significant decrease (p<0.001) in the ROM for forward flexion (10.9°, sd: 16.8) and abduction/external rotation (8.2°, sd: 15.5). No change in ROM was observed for the external rotation alone. Considerable decreased muscle strength in the shoulder abductors (18.4 Newton-meters [Nm]; sd: 31.1) and elbow flexors (15.7 Nm; sd: 41.7) was observed. Also grip strength decreased significantly with 12.1 Nm (sd: 48.3) postoperatively. The circumferences of the forearm and upper arm as measured 6 weeks after surgical treatment had not changed significantly (Table 2).

The SDQ and GARS found increased disability among the breast carcinoma patients. The change on the SDQ (15.6, sd: 30.3 [on a scoring range from 0–100]) was larger than the change assessed with the GARS (4.5, sd: 6.1 [on a scoring range from 18–72]) (Table 2). None of the assessments of the non-involved side changed significantly between t0 and t1.

The increase in perceived disability (SDQ, GARS) between t0 and t1 was significant correlated with the increase in pain and decrease of shoulder ROM and only for the GARS with loss of strength (Table 3).

Changes in forward flexion, abduction, abduction / external rotation, grip strength, strength of shoulder abductors and elbow-flexors and the GARS between t0 and t1 were significantly different between the SLNB group and the ALND group (Table 4). All of these assessed items of upper limb function and ADL changed significantly more in the ALND group compared to the SLNB group (Table 4). Numbness was observed in 14 patients in the SLND group (23 %) and in 119 patients in the ALND group (87 %) at t1 (p<0.01 Chi-Square test).

Complementary linear regression analysis to predict change in upper-limb function and ADL between t1 – t0 for independent variables axillary surgery (SLNB, ALND) and surgery of the breast (breast conserving surgery, mastectomy) was performed (Table 5). Axillary lymph node dissection and to a minor extent mastectomy were significant factors in the prediction of changes in forward flexion, abduction, abduction / external rotation, grip strength, strength of shoulder abductors and elbow-flexors and the GARS between t0 and t1 (Table 5).

Table 2. Upper limb morbidity and disability (t1-t0) 6 weeks after breast cancer treatment (n=198)

	t0 Pre-operative		t1 6 weeks postoperative		Change (t1-t0)		p
	Mean	SD	Mean	SD	Mean	SD	
Pain (VAS: 0 – 10)	0.4	1.2	1.3	2.0	.9	2.0	.000
Forward flexion (°)	172.6	11.6	161.7	18.0	-10.9	16.8	.000
Abduction (°)	167.8	22.5	142.3	34.1	-25.5	34.2	.000
Abduction / external rotation (°)	87.1	6.7	78.9	16.0	-8.2	15.5	.000
External rotation (°)	67.5	12.9	66.8	12.9	-.7	12.3	.458
Grip strength (Nm)	295.3	65.8	283.2	66.4	-12.1	48.3	.001
Strength shoulder abductors (Nm)	150.8	37.0	132.4	39.4	-18.4	31.1	.000
Strength elbow flexors (Nm)	179.6	41.5	163.9	41.1	-15.7	41.7	.000
Circumference upper arm (cm)	26.8	3.1	27.0	3.2	.2	1.3	.068
Circumference forearm (cm)	24.3	2.1	24.3	2.1	.0	.9	.758
SDQ (0-100)	8.6	20.1	24.2	30.2	15.6	30.3	.000
GARS (18-72)	19.7	3.9	24.2	6.6	4.5	6.1	.000

Abbreviations: SD: standard deviation; VAS: visual analog scale; Nm: Newton-meters; cm: centimeter; (°): degrees; SDQ: The Shoulder Disability Questionnaire[46]; GARS: The Groningen Activity Restriction Scale[48]

Table 3. Pearson correlation between upper-limb morbidity and the increase in perceived disability between t0 and t1 (n=198)

Upper-limb morbidity t1-t0	SDQ change t1-t0		GARS change t1-t0	
	Pearson Corr	Sig. (2-tailed)	Pearson Corr	Sig. (2-tailed)
Pain (VAS: 0 – 10)	.414	<0.001	.348	<0.001
Forward flexion	.367	<0.001	.471	<0.001
Abduction	.320	<0.001	.435	<0.001
Abduction / external rotation	.231	<0.001	.412	<0.001
External rotation	.121	.094	.100	.171
Grip strength	.061	.405	.198	.006
Strength shoulder abductors	.086	.238	.223	.002
Strength elbow flexors	.075	.303	.225	.002
Circumference upper arm	.063	.383	.013	.855
Circumference forearm	.099	.172	.221	.002

Abbreviations: VAS: visual analog scale; SDQ: The Shoulder Disability Questionnaire[46]; GARS: The Groningen Activity Restriction Scale[48]

Table 4. Change of upper limb function and disability in the SLNB group and the ALND group

	SLNB (t1-t0) n=62		**ALND** (t1-t0) n=136		Differences in mean change ALND-SLNB	
	Mean change	SD	Mean change	SD	Mean difference	*p*
Pain (VAS: 0 – 10)	0.6	1.9	1.0	2.0	.4	.234
Forward flexion (°)	-4.4	12.6	-13.9	17.7	9.5	.000
Abduction (°)	-8.8	29.4	-33.1	33.6	24.3	.000
Abduction / external rotation (°)	-3.7	8.8	-10.3	17.4	6.6	.001
External rotation (°)	1.2	9.5	-1.5	13.3	2.7	.106
Grip strength (Nm)	1.0	50.5	-18.1	46.2	19.1	.010
Strength shoulder-abductors (Nm)	-5.8	23.8	-24.1	32.4	18.3	.000
Strength elbow-flexors (Nm)	-2.4	32.1	-21.6	44.1	19.2	.003
Circumference upper arm (cm)	.2	.8	.2	1.6	.0	.833
Circumference forearm (cm)	-.1	1.2	.0	.8	.1	.422
SDQ (0-100)	10.4	26.9	17.9	31.5	7.5	.106
GARS (18-72)	1.6	4.6	5.8	6.2	4.2	.000

Results of t test for independent samples

Abbreviations: SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection; sd: standard deviation; VAS: visual analog scale; Nm: Newton-meters; cm: centimeters; (°): degrees; SDQ: The Shoulder Disability Questionnaire[46]; GARS: The Groningen Activity Restriction Scale[48]

Table 5. Linear regression analysis to predict change in upper-limb function and ADL between t1 – t0 for independent variables axillary surgery (SLNB=0, ALND=1) and surgery of the breast (breast conserving surgery=0, mastectomy=1)

Dependent	Independent	ß (95% CI)	r^2 change
Assessments:			
Forward flexion (°)			
	axillary surgery (0, 1)	8.3 (3.3 to 13.3)	.07
	breast surgery (0, 1)	6.0 (1.3 to 10.7)	.03
	Constant	2.8 (-1.4 to 7.0)	
Abduction (°)			
	axillary surgery (0, 1)	20.1 (10.4 to 29.8)	.07
	breast surgery (0, 1)	19.1 (9.9 to28.2)	.11
	Constant	3.8 (-4.4 to 12.0)	
Abduction / external rotation (°)			
	axillary surgery (0, 1)	5.4 (0.7 to 10.1)	.03
	breast surgery (0, 1)	5.5 (1.1 to 9.9)	.04
	Constant	2.2 (-1.8 to 6.2)	
Grip strength (Nm)			
	axillary surgery (0, 1)	1.9 (0.4 to 3.4)	.03
	Constant	0.1 (-1.3 to 1.1)	
Strength shoulder-abductors (Nm)			
	axillary surgery (0, 1)	18.6 (9.4 to 27.7)	.08
	Constant	5.8 (-1.8 to 13.5)	
Strength elbow-flexors (Nm)			
	axillary surgery (0, 1)	19.0 (6.3 to 31.6)	.04
	Constant	2.3 (-8.1 to 12.9)	
GARS (18-72)			
	axillary surgery (0, 1)	3.8 (2.0 to 5.5)	.10
	breast surgery (0, 1)	1.9 (0.2 to 3.6)	.02
	Constant	1.1 (-0.4 to 2.6)	

Only significant predictors are represented in the table.

Abbreviations: CI: confidence interval; SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection; SDQ: The Shoulder Disability Questionnaire[46]; GARS: The Groningen Activity Restriction Scale[48]

The larger the coefficient ß, the larger is the contribution of the independent variable to the explanation of the dependent variable. The r^2 change is a measure for the explained variance of the dependent variable by the independent variables. One hundred times r^2 change gives the percentage of explained variance.

Discussion

The current study showed that there is significant short-term upper limb morbidity and associated ADL disabilities in patients with breast carcinoma who undergo SLNB and/or ALND. Also significantly less short-term upper limb morbidity and ADL disabilities was found for SLNB compared to ALND.

This outcome is conforming to the assumption that SLNB, a much less extensive procedure compared with ALND, is associated with less upper-limb morbidity than ALND. To our knowledge, only three other studies have reported morbidity results after a relatively short follow-up period after SLNB and ALND.[32-34] Baron et al.[32] and Temple et al.[33] used a self-constructed instrument (i.e., the Breast Sensation Assessment Scale) to assess sensory morbidity. Although the authors reported some difference in prevalence of breast sensations between SLNB and ALND at baseline (3–15 days post surgery) and 3 months post surgery, the difference was significant for only 5 of the 18 sensations. When women reported sensations as severe or very severe, a significant difference in prevalence was only present for 3 of the 18 sensations (specifically, numbness, stiffness, and tingling).[32]

Swenson et al.[34] assessed the side effects of both procedures with a self-constructed questionnaire (i.e., the Measure of Arm Symptom Survey) at 1, 6, and 12 months post surgery. They found significant differences in perceived pain, numbness, limitation in range of motion, and interference with daily life between patients with ALND and patients with SLNB at 1 month post surgery. This difference in occurrence of side effects in favor of the SLNB patients continued at 6 and 12 months post surgery, with the exception of interference in daily life.

In contrast to the three previous studies,[32-34] the current study used a preoperative baseline assessment. In addition, several reliable and validated objective assessment tools were used and the influence of short-term upper-limb morbidity on ADL was assessed.[15,38-49] In a recent systematic review,[14] the importance of the baseline assessment against which to compare the follow-up assessment was emphasized.[14] Using this baseline assessment, possible disturbances in the cause-and-effect relation were ruled out and therefore only the postoperative changes in upper-limb function and ADL were reported.

A potential limitation in this study is that contemporary treatment options (mastectomy / breast conserving surgery) were not divided equally between the two groups (SLNB and ALND). However, the linear regression analysis showed ALND as the most important predictor for change in upper-limb function and the GARS. Mastectomy was to a lesser extent also a significant predictor of reduction in shoulder ROM and perceived disabilities in ADL. Other potential confounders such as adjuvant radiotherapy and chemotherapy had no influence on the study outcome because they were started after the post operative (t1) assessment. Because the SLNB procedure is

a relatively new technique, no data were available to perform an adequate power analysis before the current study.

Conform other studies, significant difference in prevalence of numbness between the SLNB and ALND group was documented.[26,32-35] A significant change in upper limb function and ADL after SLNB or ALND was found in the current study. However, the overall upper limb morbidity and associated disabilities in ADL were small. Impairments that significantly correlated with perceived disabilities in ADL post surgery were pain, decreased shoulder ROM and to a minor extent loss of strength (Table 3). This means that these significant but rather small mean reduction in upper limb function such as decreased shoulder ROM in forward flexion, abduction and abduction/external rotation and decreased strength of shoulder abductors, elbow flexors and grip, and the increased pain perception are clinical relevant in relation to perceived disabilities in ADL six weeks after surgery.

In conclusion, significant short-term treatment related upper limb morbidity and associated ADL disabilities exist after SLNB or ALND. Six weeks after surgery, there is significantly less upper-limb morbidity after SLNB compared to ALND. ALND as well as to a lesser extent mastectomy are predictors for short-term upper limb morbidity.

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CHAPTER 5

Treatment-related upper limb morbidity 1 year after sentinel lymph node biopsy or axillary lymph node dissection for stage I or II breast cancer

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Published
Annals of Surgical Oncology 2004;11(11):1018-24

Abstract

Background

In a prospective study, upper limb morbidity and perceived disability in activities of daily life (ADLs) were assessed before and 1 year after sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND).

Methods

A total of 204 patients with stage I/II breast cancer (mean age, 55.6 years; SD, 11.6 years) entered the study, and 189 patients (93%) could be evaluated after 1 year. Fifty-eight patients (31%) underwent only SLNB, and 131 (69%) underwent ALND. Assessments performed before surgery (t0) and 1 year after surgery (t1), included pain, shoulder range of motion, muscle strength, upper arm/forearm circumference, and perceived shoulder disability/ADL.

Results

Considerable treatment-related upper limb morbidity was observed. Significant (P <0.05) changes between t0 and t1 were found in all assessments except strength of elbow flexors. Patients in the ALND group showed significantly more changes in the range of motion in forward flexion, abduction, and abduction/external rotation; grip strength and strength of shoulder abductors; circumference of upper arm and forearm; and perceived shoulder disability in ADLs compared with the SLNB group. Multivariate linear regression analysis showed that ALND could predict a decrease of range of motion in forward flexion, abduction, strength of shoulder abductors, grip strength, and shoulder-related ADLs and an increase in the circumference of the upper arm. Radiation of the axilla (19 patients) predicts an additional decrease in shoulder range of motion.

Conclusions

One year after treatment of breast cancer, there is significantly less upper limb morbidity after SLNB compared with ALND. ALND is a predictor for upper limb morbidity.

Introduction

The aim of modern breast cancer treatment is to obtain local tumor control, optimal lymph node staging with minimal treatment related morbidity, good functional results and when possible, preservation of the breast. Axillary lymph node status is an important prognostic factor in patients with breast cancer.[1-4] Axillary lymph node dissection (ALND) however, is associated with upper limb morbidity such as pain, numbness, lymph edema, weakness and impaired shoulder range of motion.[5-12] Upper limb morbidity can affect the ability to perform activities of daily life (ADLs) and quality of life (QOL).[11-18]

Sentinel lymph node biopsy (SLNB) was introduced for staging of the axilla to reduce the number of unnecessary ALNDs.[19] SLNB is an accurate and safe procedure to predict metastatic disease in axillary lymph nodes and is widely accepted in breast cancer treatment.[19-23] SLNB is an excellent alternative for ALND in patients with clinically negative lymph nodes.[24] An increasing number of studies have evaluated SLNB related morbidity in comparison with ALND related morbidity.[22,23,25-35] Most of these studies reported less morbidity for SLNB than for ALND.[23,25-36] A shortcoming in most studies is the absence of pre-treatment assessment.

Fewer studies have investigated upper limb morbidity and perceived disability in ADLs after SLNB in comparison to ALND.[26,30,33] Generally, disability in ADLs of the SLNB group was less than for the ALND group.[26,30,33]

The aim of this study was to analyze prospectively the upper limb morbidity and perceived disability in ADLs of patients 1 year after SLNB versus ALND. Secondarily, it analyzed to which extent ALND and other treatment variables could predict upper limb morbidity and perceived disability.

Patients and methods

From June 1999 to June 2001, patients with breast carcinoma stage I or stage II participated in the study.[37] Patients were recruited from the University Hospital Groningen and the Martini Hospital Groningen. Informed consent was obtained from the participating patients. The protocol was approved by the Institutional Review Board of both hospitals. Two groups of breast cancer patients participated in the prospective study; patients who underwent conventional breast cancer treatment with ALND and patients who were treated according to the SLNB concept. Patients with positive sentinel lymph nodes subsequently received an ALND and were included in the ALND group.

Sentinel lymph nodes were identified by pre-operative lymphoscintigraphy followed by intra-operative tracing with a gamma probe and Patent blue dye® (Blue Patenté; Labatoire Guerbet, Aulnay-sous-Bois, France). The procedure has been

previously described in detail.[38] If pathological examination revealed metastases in the sentinel lymph node, ALND was performed within 2 weeks after SLNB. Surgical and adjuvant treatments were used according to our protocol in both groups (Table 1).

Upper limb function and ADLs were assessed 1 day before surgery (t0) and one year after surgery (t1). Pain was assessed with the visual analogue scale (VAS; Table 2). Patients were asked to mark their current pain on a 10 cm straight line (0 cm = no pain, 10 cm = worst pain imaginable).[39,40] Upper limb function was assessed by means of a physical examination according to a protocol (Table 2). Active shoulder range of motion was measured with a goniometer (Isomed® Inclinometer; Portland, Oregon, USA) according to a standardized protocol in forward flexion, abduction and external rotation.[40,41] Muscle strength of shoulder abductors and elbow flexors were measured using a handheld dynamometer (Citec®, Groningen, The Netherlands).[42-44] For assessment of the grip strength, a Yamar® hand-dynamometer (Bollingbrook, Ilinois, USA) was used.[45,46] All muscle strength measurements were performed three times and the mean of these three measurements was used for further analysis. Upper and forearm circumferences were measured using a Gulick Measuring Tape® (Lafayette Instruments; model 258-J00305, Lafayette, Indiana, USA) at 10 cm proximal to the olecranon and 15 cm proximal to the styloid process of the ulnae.

ADLs were assessed with the Shoulder Disability Questionnaire (SDQ) and the Groningen Activity Restriction Scale (GARS).

The SDQ is a functional status measure that covers 16 items. It was designed to evaluate the ability to perform daily activities in patients with shoulder disorders (shoulder related ADLs).[47,48] It contains 16 statements that patients with shoulder disorders have used, to describe in what kind of ADL situations they experience pain. It has a three-category response format; for example; 1, "Yes my shoulder is painful when I open or close a door"; 2, "No my shoulder is not painful when I open or close a door"; 3, "I did not perform the activity during the past 24 hours". The total scoring range for the 16 statements was transformed to 0-100. Score of 0 means no functional status limitation and a score of 100 means maximum functional status limitation (Table 2).[47,48]

The GARS assesses the perceived restrictions (disability) in performing 18 ADLs.[49,50] It has a four-category response format: 1, able to perform the activity without any difficulty; 2, able to perform the activity with some difficulty; 3, able to perform the activity with much difficulty; 4, unable to perform the activity independently. The sum scoring range is 18-72. With a score of 18 the person can perform all the activities without any difficulty; with a score of 72 the person cannot perform any activity without the help of others (Table 2).[49,50]

Statistical analyses included descriptive statistics and *t*-tests for independent samples for between-group comparisons and *t*-tests for dependent samples for within-group comparisons. Pearson's χ^2 test was used for dichotomous variables. To discern to what extent treatment variables could predict upper limb morbidity and perceived

disability, multivariate linear regression analyses were performed with the following independent variables: ALND, surgical treatment of the breast (modified radical mastectomy or lumpectomy), radiation of the axilla, and radiation of the breast. Differences were accepted as significant if P values were <0.05.

Table 1. Tumor-node-metastasis classification, receptor status and treatment characteristics of the included patients

	SLNB (n=66)	**ALND** (n=138)	**Total** (n=204)
Patient age, y, mean (SD)	57.0 (11.9)	54.9 (11.3)	55.6 (11.6)
TNM classification:			
Stage I	46 (70)	39 (28)	85 (42)
Stage IIA	15 (23)	71 (51)	86 (42)
Stage IIB	5 (8)	28 (20)	33 (16)
Estrogen-receptor status:			
Positive	38 (58)	96 (70)	134 (66)
Negative	28 (42)	42 (30)	70 (34)
Surgical treatment breast:			
Mastectomy	17 (26)	68 (49)	85 (42)
Lumpectomy	49 (74)	70 (51)	119 (58)
Adjuvant therapies:			
Radiotherapy breast	49 (74)	70 (51)	119 (58)
Radiotherapy axilla	0 (0)	19 (14)	19 (9)
Chemotherapy	10 (15)	59 (43)	69 (34)
Hormonal therapy	10 (15)	68 (49)	78 (38)

Abbreviations: Data are n (%) unless otherwise noted.
SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection

Table 2. Assessment of shoulder function and activities of daily life (ADLs)

Assessment	Assessment tool
Shoulder function:	
Pain (current pain)	VAS[39,40] *(cm)*
Numbness	Clinical examination: numbness *yes* or *no*
Active shoulder range of motion:	Isomed® Inclinometer.[40,41] *(°)*
Forward flexion	
Abduction	
Combined abduction/external rotation	
External rotation	
Muscle strength:	Citec® handhold dynamometer.[42-44] *(Nm)*
Shoulder abductors	
Elbow flexors	
Grip strength (cilinder grip)	Yamar® hand-dynamometer.[45,46] *(Nm)*
Circumference	
Upper arm circumference	Gulick Measuring Tape (Lafayette Instrument;
(10 cm proximal to the olecranon)	model 258-J00305) *(cm)*
Fore arm circumference	
(15 cm proximal to the processus styloideus ulnae)	
ADL	SDQ[47,48]
	GARS[49,50]

Abbreviations: VAS: visual analogue scale; cm: centimeters; (°): degree; Nm: Newton meter; SDQ: The Shoulder Disability Questionnaire[47,48]; GARS: The Groningen Activity Restriction Scale[49,50]

Results

From 1999 to 2001, 204 consecutive patients with invasive breast carcinoma were included in the study. Initially 124 patients (61%) underwent a SLNB. 58 patients (47%) subsequently underwent additional ALND because of metastasis in the sentinel node. Therefore the study consisted of 66 patients (32%) with a SLNB and 138 patients (68%) with a level I-II ALND. Tumor-node-metastasis classification, receptor status and treatment characteristics of the patients are listed in Table 1. At t1, 189 patients could be evaluated; 58 patients (31%) in the SLNB group and 131 patients (69%) in the ALND group. Fifteen patients (7%) could not be assessed after 1 year. Seven patients from the ALND group; two patients died of metastatic disease; two withdrew from the study because of distant metastases and three withdrew because of psychological burden. Eight patients belonged to the SLNB group; one patient had distant metastasis, one patient refused further treatment, and six found the assessment

protocol bothersome and chose to withdraw from the study although they had no upper limb complaints.

After one year substantial treatment related upper limb morbidity was observed for the entire study group (n=189). Significant changes between t0 and t1 were found in all assessments except strength of the elbow flexors (Table 3). There was a small but significant increase in self-assessed pain perception (VAS) from 0.4 (SD, 1.1) to 0.8 (SD, 1.5). Numbness of the axillary region was observed in 119 patients (63%). The largest decrease in range of motion of the shoulder was found in abduction (15.7°; SD, 28.8). Decrease in grip strength (16.8 Nm, SD, 48.0) and muscle strength of the shoulder abductors (11.4 Nm; SD, 31.9) were observed. At t1, there was a minor but significant increase of upper arm circumference (0.7 cm; SD, 1.7) and forearm circumference (0.4 cm; SD, 1.0).

Disability in ADLs increased as assessed with the SDQ (10.7; SD, 29.2) and the GARS (1.5; SD, 4.6; Table 3).

Several changes in upper limb function (upper limb morbidity) and ADLs (perceived disability) between t0 and t1 were significantly different between the SLNB group and the ALND group, in favor of the first (Table 4).

No significant difference was found for the change in pain perception of both groups (Table 4). Numbness was observed in 10 patients (17%) in the SLNB group and in 109 patients (83%) of the ALND group at t1 ($p<.001$ χ^2 test). For range of motion of the shoulder, the largest difference was found in shoulder abduction (14.5°; 95% confidence interval [CI], 22.0° to 7.1°; Table 4). No difference was found in the external rotation between the groups. Significant differences were observed for grip strength (25.6 Nm; 95% CI, 40.8 to 10.3 Nm), strength of shoulder abductors (14.9 Nm; 95% CI, 23.5 to 6.3 Nm) and, to a minor extent, strength of the elbow flexors (Table 4). The differences in circumference of the upper arm and forearm were significant (upper arm: .6 cm; 95% CI: .1 to 1.1, forearm: .3 cm; 95% CI: .1 to .6) (Table 4).

Considering the increase in perceived disability in ADLs, a significant difference between the SLNB group and the ALND group was found for the SDQ (10.6; 95% CI: 2.5 to 18.7) but not for the GARS (1.0; 95% CI: -.1 to 2.1).

Multivariate linear regression analysis was performed to predict the mean change in upper limb function and ADLs between t0–t1 for independent variables axillary surgery (SLNB and ALND), surgery of the breast (breast conserving surgery and mastectomy), radiation of the breast (no or yes), and radiation of the axilla (no or yes) (Table 5). ALND was a significant factor in the prediction of almost all mean changes in the performed assessments of upper-limb function and ADLs (Table 5). Radiation of the axilla was also significant in four analyses (Table 5).

Table 3. Upper limb morbidity and disability (t1-t0) 12 months after breast cancer treatment (n=189)

Variable	Before surgery (Mean ± SD)	12 mo after surgery (Mean ± SD)	Change (t1-t0) (Mean ± SD)	p
Pain (VAS: 0 – 10)	0.4 ± 1.1	0.8 ± 1.5	0.4 ± 1.7	.001
Numbness (n)*	0	119	119	<0.001
Forward flexion (°)	172.5 ± 11.8	166.3 ± 14.1	-6.2 ± 12.9	<0.001
Abduction (°)	167.7 ± 22.7	152.0 ± 31.7	-15.7 ± 28.8	<0.001
Abduction / external rotation (°)	87.0 ± 6.8	79.4 ± 14.4	-7.6 ± 13.4	<0.001
External rotation (°)	67.7 ± 12.9	61.7 ± 12.7	-6.0 ± 12.6	<0.001
Strength shoulder abductors (Nm)	150.9 ± 36.8	139.5 ± 36.8	-11.4 ± 31.9	<0.001
Strength elbow flexors (Nm)	179.5 ± 41.2	179.5 ± 38.0	0.0 ± 40.3	.999
Grip strength (Nm)	296.1 ± 65.1	279.3 ± 71.0	-16.8 ± 48.0	<0.001
Circumference upper arm (cm)	26.8 ± 3.0	27.5 ± 3.2	0.7 ± 1.7	<0.001
Circumference forearm (cm)	24.3 ± 2.1	24.7 ± 2.2	0.4 ± 1.0	<0.001
SDQ (0-100)	7.9 ± 19.3	18.6 ± 27.9	10.7 ± 29.2	<0.001
GARS (18-72)	19.7 ± 3.8	21.2 ± 5.2	1.5 ± 4.6	<0.001

Abbreviations: VAS, visual analog scale; SDQ, The Shoulder Disability Questionnaire[47,48]; GARS: The Groningen Activity Restriction Scale[49,50]; Nm, Newton meter
* No standard deviations were given because it concerns a dichotomy variable

Table 4. Change of upper limb function and disability in the SLNB group and the ALND group between t1 (12 months after surgery) and t0 (before surgery)

Variable	SLNB (n=58) (t1-t0) (Mean change ± SD)	ALND (n=131) (t1-t0) (Mean change ± SD)	Differences in mean change, ALND-SLNB (Mean difference)	p
Pain (VAS: 0 – 10)	0.2 ± 1.2	0.6 ± 1.9	0.4	.073
Numbness (n)*	10	109	99	<0.001
Forward flexion (°)	-2.7 ± 10.0	-7.7 ± 13.7	5.0	.005
Abduction (°)	-5.6 ± 20.2	-20.1 ± 30.9	14.5	<0.001
Abduction / external rotation (°)	-4.6 ± 7.9	-8.9 ± 15.0	4.3	.011
External rotation (°)	-4.6 ± 12.3	-6.6 ± 12.8	2.0	.324
Strength shoulder-abductors (Nm)	-1.0 ± 24.0	-15.9 ± 33.9	14.9	.001
Strength elbow-flexors (Nm)	7.5 ± 28.3	-3.3 ± 44.3	10.8	.048
Grip strength (Nm)	0.0 ± 45.9	-25.6 ± 50.0	25.6	.001
Circumference upper arm (cm)	0.3 ± 1.2	0.9 ± 1.8	0.6	.019
Circumference forearm (cm)	0.2 ± 0.7	0.5 ± 1.0	0.3	.009
SDQ (0-100)	3.4 ± 23.5	14.0 ± 31.0	10.6	.011
GARS (18-72)	0.8 ± 2.2	1.8 ± 5.4	1.0	.065

Results of t test for independent samples
Abbreviations: SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; VAS, visual analog scale; SDQ, The Shoulder Disability Questionnaire[46]; GARS: The Groningen Activity Restriction Scale[48]; Nm, Newton meter; cm, centimeter; (°), degree; * No standard deviations were given because it concerns a dichotomy variable

Table 5. Prediction of mean change in upper-limb function and ADL between t0 – t1 by means of linear regression analysis for independent variables: axillary surgery (SLNB=0, ALND=1), surgery of the breast (breast conserving surgery=0, mastectomy=1), radiation breast (no=0, yes=1) and radiation axilla (no=0, yes=1)

Dependent	Independent	ß (95% CI)	r^2 change
Assessments:			
Forward flexion (°)			
	ALND	4.9 (0.9-8.9)	.03
	Constant	2.7 (-0.6-6.0)	
Abduction (°)			
	Radiation of axilla	19.5 (5.0-34.1)	.05
	ALND	11.6 (2.8-20.4)	.03
	Constant	5.6 (-1.5-12.7)	
Abduction / external rotation (°)			
	Radiation of axilla	7.4 (0.7-14.2)	.03
	Constant	6.8 (4.8-8.7)	
External rotation (°)			
	Radiation of axilla	7.2 (0.8-13.6)	.03
	Constant	5.1 (3.3-7.0)	
Strength of shoulder-abductors (Nm)			
	ALND	14.1 (4.4-23.8)	.04
	Constant	1.0 (-7.1-9.1)	
Grip strength (Nm)			
	ALND	24.3 (9.3-39.3)	.05
	Constant	-0.9 (-13.3-11.6)	
Circumference of upper arm (cm)			
	ALND	-0.6 (-1.2-0.2)	.03
	Constant	-0.3 (-0.7--0.1)	
Circumference of forearm (cm)			
	Radiation of axilla	-0.6 (-1.1--0.1)	.03
	Constant	-0.4 (-0.5--0.2)	
Shoulder Disability Questionnaire			
	ALND	-11.9 (-20.9--2.9)	.03
	Mastectomy	9.1 (0.5-17.6)	.02
	Constant	-6.0 (-13.8-1.7)	

Only significant predictors are represented.

Abbreviations: SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; CI, confidence interval.

The larger the coefficient ß, the larger are the contribution of the independent variable to the explanation of the dependent variable. The r2-change is a measure for the explained variance of the dependent variable by the independent variables. One hundred times r^2-change gives the percentage of explained variance. For instance; Constant is the mean change in the ROM Abduction when a patient received SLNB. When a patient received ALND the mean ROM Abduction decreased another 11.6° and when this patient received also radiation on the axilla the mean ROM Abduction decreased another 19.5° (ΔAbd= C + (0,1)ALND x 11.6 + (0,1)rad axilla x 19.5).

Discussion

This study showed significant upper limb morbidity and associated ADL disabilities 1 year after treatment in breast cancer patients undergoing SLNB, ALND or both. Patients undergoing SLNB had significantly less upper-limb morbidity and fewer ADL disabilities 1 year after treatment compared with patients undergoing ALND.

This outcome confirms the assumption that SLNB is a less extensive surgical procedure that is associated with less upper limb morbidity compared with ALND. Several studies previously reported on morbidity after SLNB and ALND.[23,25-35] All studies reported less morbidity in patients after SLNB compared with ALND. However, there was considerable variability in study design. Only four studies used a pre-operative assessment.[25,29,32,34] The follow-up period varied from 2 weeks to 3 years after surgical treatment.[32,33] Also, the assessment instruments varied from self constructed questionnaires to physical examination and some validated questionnaires. ADL was assessed in only two studies.[26,30]

This study used a pre-operative assessment. Additionally several reliable and validated measurement instruments were used to assess upper limb morbidity and perceived disabilities in ADL.[40-42,44,46,48,49] In a recent systematic review, we emphasized the importance of the baseline assessment.[12] Pre-operative assessment was also used by Leidenius et al.[32] and Peintinger et al.[34] The first study mentioned, evaluated shoulder range of motion before, 2 weeks and 3 months after surgery.[32] Difference in the prevalence of axillary web syndrome (20% of patients with SLNB, 72% of patients with ALND) were held responsible for the difference in range of motion. Contrary to our findings, a normal range of motion was observed in almost all patients of both groups after 3 months. In that study, the author described only short-time morbidity.[32] Peintinger et al.[34] evaluated pain, range of motion and perceived disability (Karnofsky performance status scale [KPS]), in addition to QOL before, to 1 year after ALND/SLNB. Similar to our results, they found significantly more pain (VAS), numbness, and change of abduction and flexion in the ALND group 1 year after treatment. In contrast to our results, patients perceived no disabilities (KPS) 1 year after treatment.[34] Maybe this was caused by their relative small patient sample size (n=56) or the different assessment instrument (KPS versus SDQ/GARS). The KPS might be less sensitive for detecting small changes. Swenson et al.[30] assessed the side effects of ALND and SLNB with a self-constructed questionnaire (the Measure of Arm Symptom Survey) at 1, 6 and 12 months after surgery. At 12 months they found significant differences in perceived pain, numbness and limitation in range of motion in favor of the SLNB patients but found no difference between groups in interference with daily life.[30] The perceived disabilities in ADLs assessed in our study were relatively mild. Shoulder related perceived disabilities assessed by the SDQ were significantly higher in the ALND group compared with the SLNB group. This

significant difference was not found for the GARS. Probably the effect of axillary dissection is stronger for shoulder related disabilities in ADL than for disability in ADLs in general.

The SLNB group had a more favorable outcome than the ALND group with respect to adjuvant radiation on the axilla, chemotherapy and hormonal therapy (Table 1). Relatively few ALND patients (19 of 138; 14%) received radiation on the axilla. Other studies reported effects of radiation on the axilla on shoulder range of motion.[12,18,45,51,52] The fact that patients who received radiation on the axilla naturally belonged to the ALND group may influence the comparison between SLNB and ALND concerning treatment related morbidity.

Multivariate linear regression analysis to predict mean change in upper limb function and ADLs between t0 and t1 showed that ALND and radiation on the axilla were significant factors in the prediction of impaired range of motion (Table 5). Clinically, these findings indicate that concerning the decrease in range of motion in shoulder abduction, SLNB was responsible for 5.6° of the reduction, ALND was responsible for another 11.6°, and radiation on the axilla for another 19.5°. The effect of radiation on the axilla was most noteworthy for shoulder abduction, combined abduction/external rotation, and external rotation. These results suggest that radiation on the axilla affects the shoulder range of motion more than it affects muscle strength (Table 5). This is conform results of some other studies[12,18,52] and may be explained by radiation induced subcutaneous fibrosis affecting the range of motion.

ALND as a predictor of upper limb morbidity was observed for forward flexion, abduction, strength of shoulder abductors, grip strength, upper arm circumference, and shoulder related ADLs (SDQ). These results confirm those of other studies in which the extent of axillary treatment was related to late morbidity.[12,15,33,52]

Conclusion

Significant treatment related upper limb morbidity and associated ADL disabilities exist 1 year after SLNB or ALND. Treatment related morbidity and shoulder related perceived disabilities in ADL (SDQ) are significantly lower 1 year after SLNB compared with ALND. ALND can predict upper limb morbidity and shoulder related perceived disabilities in ADL. Additional radiation on the axilla predicts a further decrease in shoulder range of motion.

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CHAPTER 6A

Phantom breast sensations and phantom breast pain
Part 1
A 2-year prospective study

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Submitted

Abstract

The aim of this study was to assess prospectively the incidence of phantom breast sensations (PB sensations) and phantom breast pain (PB pain) in a sample of 82 Dutch mastectomy patients and to assess how much they are bothered by PB sensations and PB pain.

Patients were assessed 6 weeks, 6 months, 1 year and 2 years after mastectomy, by means of a questionnaire. After 2 years, assessments of 74 patients were available.

Two years after mastectomy, PB sensations were present in 19% (n=14) of the patients and PB pain was present in 1% (n=1) of the patients. Patients were hardly bothered by PB sensations or PB pain. Over time the percentage of patients with PB sensations remained relatively stable (around 20%) but for PB pain the percentage reduced from 7% to 1%.

PB sensations and PB pain are of little clinical relevance in the 2 years following mastectomy.

Introduction

The incidence of breast cancer in the Netherlands is 127 / 100.000 women per year. [1] One out of ten women will develop breast cancer, of which 79% will survive at least five years.[1,2] The aim of breast cancer treatment is to obtain local tumor control, optimal lymph node staging with minimal treatment related morbidity, good functional result and if possible preservation of the breast. Post treatment morbidity of breast cancer patients includes reduced range of motion of the shoulder, swelling of the arm, and a reduced shoulder strength or grip strength.[3,4]

Additionally 55% of the women may experience some type of pain after breast cancer treatment.[5] Different types of pain have been found after treatment of breast cancer including scar pain, neuropathic pain, neuroma pain and complex regional pain syndrome. [6-8] Neuropathic pain is the result of resection or damage to the intercostobrachial nerve after axillary lymph node dissection and it may be felt in the axilla or in the medial part of the arm. Pain due to neuroma may develop after resection of nerves that attempt to regenerate to their target organ but fail and develop a tangle of axons. These neuromas usually develop in scars.

After mastectomy, patients may experience sensations or pain as coming from the amputated breast, known as phantom breast sensations (PB sensations) and phantom breast pain (PB pain).[9,10] PB sensations are all those sensations that are experienced in the amputated breast whereas PB pain are all those sensations that are experienced in the amputated breast that are so intense that they are experienced as pain. The variation of prevalence of PB sensations and PB pain reported is substantial, ranging from 10% to 66% for PB sensations and from 0% to 53% for PB pain (Table 1).[9-37] These differences in outcomes may be attributed to research method, research design, and differences in study population. Some studies used questionnaires and others interviewed the patients to assess the presence of PB sensations or PB pain. The large majority of studies were cross-sectional and only 5 studies were prospective of which only two exceed a 1-year follow-up (Table 1).[10,27,32,34,37] The study populations differed considerably; inpatients just being operated, outpatients coming for regular appointment, a mixture of the previously mentioned groups, or volunteers for help groups of cancer patients ("Reach to Recover" or "Women for Women"). In some studies it is not clear where the patients were recruited from.[12,13,20,23,33] Women with different ages have been investigated, although the descriptive statistics in the papers do no allow adequate comparison (Table 1).

Further the impact of PB sensations or PB pain as described is highly variable. Some authors report that PB sensations and PB pain after mastectomy are minor issues in the process of coping with mastectomy while others state that PB sensations and PB pain are highly disturbing phenomena.[11,16,18,22]

The aim of this study was to assess the incidence of PB sensations and PB pain sensations in a sample of Dutch post mastectomy patients and to assess whether patients are bothered by PB sensations and PB pain in a 2-year prospective study.

Material and methods

In the period June 1999-June 2001, patients with breast carcinoma stage I or stage II were asked to participate in a cohort study.[38] From this group, all patients were selected who underwent a modified radical mastectomy. Patients were recruited from two hospitals, the University Hospital Groningen and the Martini Hospital Groningen. Informed consent was obtained from the participating patients. The Institutional Review Board (IRB) of both institutions approved the protocol. Data regarding treatment characteristics were collected from the medical records.

Pain was assessed prior to surgery by means of a 10 cm Visual Analogue Scale (VAS). The patient was asked to mark their intensity of pain, of the last week on a 10 cm straight line (0 cm = no pain, 10 cm = worst pain imaginable). Three VASs were used for average, least and worst pain of the last week. Additionally patients were asked to fill out the EORTC QLQ-C30 and the QLQ-BR23 questionnaires.[39]

PB sensations and PB pain were assessed by means of a questionnaire. This questionnaire was given to the patients to fill out while the interviewer remained present to answer any questions. The questionnaire was based upon the one used previously to investigate phantom limb pain. [40,41] Patients were assessed at 6 weeks, 26 weeks, 1 year and 2 years after mastectomy. The questionnaire assesses frequency of PB sensations and PB pain and the amount of bothering associated with PB sensations and PB pain. As risk factors for PB sensations and or PB pain the following therapy related variables were analyzed by means of chi square analyses; type of dissection (SLNB, ALND, left or right sided mastectomy, postoperative infections (yes, no), seroma production (yes, no), radiotherapy (yes, no), axillary radiotherapy (yes, no), chemo-therapy (yes , no), and loss of sensory function of the axilla (yes, no).

Additionally as pre-mastectomy risk factors, intensity of pain, average, least and worst pain prior to the mastectomy, age at mastectomy, scores of the EORTC QLQ-C30 and the QLQ-BR23 prior to the mastectomy were analyzed using t-tests for independent samples or non parametric tests. Because of multiple comparisons, 34 for PB sensations as well as PB pain, a Bonferroni-Holm correction was applied.

Table 1. Overview of the papers published concerning phantom breast sensations and phantom breast pain

Author	Publication year	Population	Age (yrs)	Design	Method	Interval	% PBS	% PBP
Crone- Münzebrock[11]	1950	in & out patients	-	c	q	few days to > 5 yrs	49	27
Ackerly[12]	1955	-	30 - 66	c	i	7 months to 9 yrs	22	4
Critchley [13]	1955	-	-	c	i	-	10	-
Bressler[14]	1956	in & out patients	-	c	i	few days to 15 yrs	64	20
Simmel[15]	1966	in & out patients	28 - 81	c	i	4 days to 18 yrs	40	-
Jarvis[16]	1967	out patients	27 - 86	c	q	-	23	8
Weinstein[17]	1970	in & out patients	21 - 87 $	c	i	1 day to 33 yrs	33	8
Jamison[18]	1979	W for W and ACS #	32 - 70	c	q	median 10 months	54	44
Moore[20]	1981	-	-	c	i	-	33	-
Christensen[19]	1982	out patients	≤45	c	i	6 to 21 months	35	6
Lorenzoni[33]	1982	-	-	c	i	-	17	0
Abraham[21]	1983	out patients	26 - 80	c	i	3 months to 17 yrs	51	5
Nail[23]	1984	-	31 - 86	c	q	1 to 25 yrs	66	-
Downing[22]	1984	out patients	33 - 97	c	i	mean 2.6 yrs (sd:2.2)$$	30	7
Staps[24]	1985	out patients	33 - 89	c	q	mean 5.3 yrs	33	24
Taylor[25]	1985	private oncology practice out patients	29 - 78	c	i	2 to 60 months	12	-
Karydas[26]	1986	out patients	52.6(sd 1.3)	c	q	1 to 36 months	55	-
Lierman[27]	1988	R to R##	63.6 (sd 7)	p	i	1 to 12 months	60	-
Kroner[10]	1992	out patients	54, IQR 45 - 62	p	i	6 yrs	26	17
Polinsky[29]	1994	R to R of 5 ACS Units ###	31 - 76	c	q	1.3 to 32 yrs	36	-
Aglioti[28]	1994	in & out patients*	35 - 78	c	i	2 days to 12 yrs	40	-
Poma[30]	1996	out patients	30 - 89	c	q	2 to 16 yrs	30	3
Tasmuth[32]	1996	out patients	29 - 85	p	i	1 year	25	-
Tasmuth[31]	1999	out patients	< 70	c	q	1 year	52	-
Baron[35]	2000	out patients	25 - 82	c	q	<1month	34	-
Baron[34]	2004	out patients	>18	p	q	2 yrs	30	-
Rothemund[36]	2004	out patients	55(sd 11.6)	c	i	8 months to 25 yrs	28	23
Reuben[37]	2004	out patients**	>18	p	i	6 months	-	53
Dijkstra (current study)	-	out patients	55.6 (sd 12.8)	p	q	2 yrs	19	1

Abbreviations: Population: population from which patients were recruited , Age: age range to which the research sample was restricted , Design: study design, Method: assessment method, Interval: Interval between surgery and investigation in cross sectional studies and in prospective studies the interval over which the study was performed, PBS: phantom breast sensations, PBP: phantom breast pain, c: cross sectional study, p: prospective study, q: questionnaire, i: interview #: Half of the patients came from Women for Women self help recovery group and the other half cam from the American Cancer Society , ##: Patients were recruited from the Reach to Recovery program of the American Cancer Society Units, ###: Patients were recruited from the Reach to Recovery volunteers of five American Cancer Society Units, -: not reported /not investigated, *: subjects who received quandrantectomy were excluded, **: The subjects were patients receiving a mastectomy in a control group of a RCT, $: at the time of mastectomy, $$: pooled data , IQR: Interquartile range. Of the prospective studies the last recorded prevalence is entered in the table.

Results

During two years (1999-2001), 204 consecutive patients with invasive breast carcinoma, mean age 55.6 (sd: 11.6) yrs, stage I (n=85; 42%), stage IIa (n=86; 42%) and stage IIb (n=33; 16%) entered the study. Six patients cancelled follow-up appointments before the 6-week assessment. One patient was treated elsewhere and excluded from the study. One patient withdrew because of distant metastases. Four patients found the assessment protocol bothersome and chose to withdraw from the study.

Thus, 198 patients completed pre- and the first postoperative assessments of which 82 received a modified radical mastectomy (mean age 56.6, sd 12.8).[38] These patients were asked to fill out the questionnaire. Treatment related characteristic are summarized in Table 2. After the first follow-up (6 weeks), 1 patient has died and 1 patient did not want to participate anymore. After the second follow-up (26 weeks), 1 patient has died and 1 patient did not want to participate anymore. After the third follow-up (1 year), another patient has died and 1 patient did not want to participate anymore and 1 patient could not be reached. One questionnaire was not filled out correctly making the number available questionnaires 74 at 2 year follow-up.

Phantom breast sensations, phantom breast pain

The percentage of patients experiencing PB sensations was more or less constant (about 20%) except 1 year after surgery (14%) and the number of patients experiencing PB pain gradually reduced from 7% to 1% (Table 3). The amount of bothering as a result of PB sensations or PB pain was low. The percentage of patients who had experienced PB sensations during some time in the two-year period (2-year prevalence) after mastectomy was 36%. For PB pain this percentage was 13%.

Risk factors

None of the possible related factors was significantly associated with PB sensations or PB pain (Tables 4 and 5).

Table 2. Treatment related characteristics for 82 women who received a mastectomy because of breast cancer

	% (n)*
Side of mastectomy	
-left	39 (31)
-right	61 (49)
-bilateral	-
Loss of sensory function axilla	77 (63)
Radiotherapy**	23 (19)
-chest wall	22 (18)
-axilla	13 (11)
Treatment axilla	
-SLNB	21 (17)
-ALND	80 (65)
Seroma	16 (12)
Infections***	6 (6)
Chemotherapy	38 (31)

Abbreviations: *Data were not available for all patients thus the number of valid observations is sometimes less than 82. **In total 19 patients received radiotherapy of which 18 received radiotherapy to the chest wall and 11 received it to the axilla. ***Infections needing treatment with antibiotics.

Table 3. Phantom breast sensations and phantom breast pain at 6 weeks, 6 months, 12 months and 24 months

Time after mastectomy (n)	6 weeks (82)	6 months (80)	12 months (78)	24 months (74)	Total period
Phantom breast sensations					
a few times a year	2	3	6	9	
a few times a month	5	5	3	3	
a few times a week	7	4	1	-	
a few times a day	2	1	-	-	
a few times per hour	-	1	-	-	
Always	2	2	1	2	
Present but freq. unknown	-	-	1	-	
Total	22% (18/82)	20% (16/80)	14% (12/78)	19% (14/74)	36% (27/74)
95% CI of total	14 to 32	13 to 30	9 to 25	12 to 29	26 to 48
New cases/reappearance	18/-	7/-	1/2	2/1	
Bothered because PBS		*			
Much	-	-	-	-	
Moderate	1	-	-	-	
Little	6	6	6	5	
No	11	9	6	9	
Phantom breast pain					
a few times a year	1	1	1	1	
a few times a month	2	-	1	-	
a few times a week	1	4	-	-	
a few times a day	2	-	-	-	
a few times per hour	-	1	-	-	
Always	-	-	-	-	
Total	7% (6/82)	8% (6/80)	3% (2/78)	1% (1/74)	13% (9/74)
95% CI of total	3 to 15	4 to 15	1 to 9	0.2 to 7	7 to 22
New cases	6	4	-	-	
Bothered because PBP			**		
Much	-	-	-	-	
Moderate	1	1	-	-	
Little	4	4	1	1	
No	1	1	-	-	

Abbreviations: *One patient with phantom sensations did not fill out the amount of bothering.
**One patient with phantom pain did not fill out the amount of bothering.

Table 4. Treatment related factors and phantom breast sensations and phantom breast pain

		PBS	p	PBP	p
Treatment axilla	ALND	35%	0.525	11%	0.772
	SLNB	24%		18%	
Mastectomy	Left	29%	0.341	7%	0.340
	Right	39%		16%	
Infections	Yes	50%	0.631	33%	0.433
	No	33%		13%	
Seroma	Yes	33%	1.000	0%	0.434
	No	31%		13%	
Radiotherapy	Yes	32%	1.000	16%	0.884
	No	33%		11%	
Chemotherapy	Yes	42%	0.293	7%	0.356
	No	28%		16%	
Loss of sensory function (axilla)	Yes	38%	0.168	6%	0.571
	No	17%		14%	

Abbreviations: ALND, Axillary lymph node dissection; SLNB, Sentinel lymph node biopsy; PBS, Phantom breast sensations; PBP, Phantom breast pain; p, significance of the differences in percentages, results of χ^2 test.

Table 5. Potential risk factors for phantom breast sensations and phantom breast pain

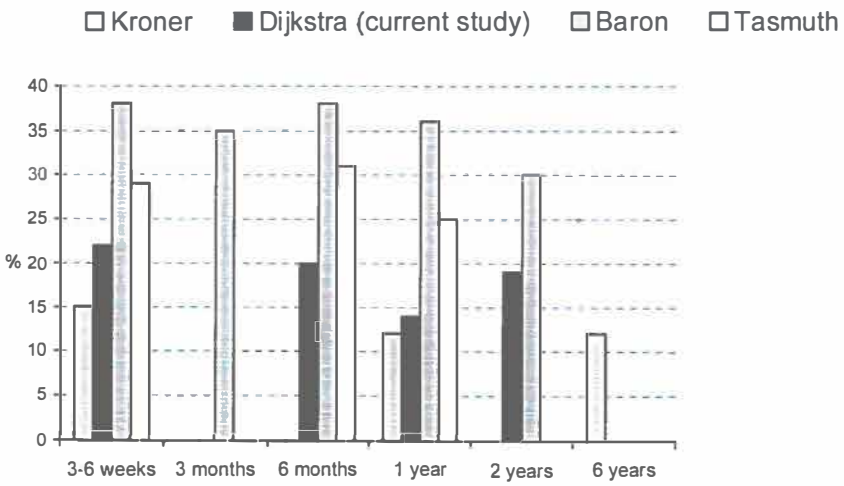
	PBS no	PBS yes	p	PNP no	PBP yes	p
	Mean(sd)	Mean(sd)		Mean(sd)	Mean(sd)	
Number of children	2.0(1.3)	2.0(1.2)	0.953	2.0(1.3)	1.8(1.4)	0.585
Age at mastectomy	58.2(12.9)	53.3(12.4)	0.102	56.5(13.4)	56.9(8.9)	0.936
VAS current	0.2(0.6)	0.6(1.4)	0.111	0.3(0.9)	0.4(1.2)	0.763
VAS least	0.1(0.5)	0.1(0.4)	0.967	0.1(0.4)	0.2(0.6)	0.667
VAS maximum	0.4(1.0)	1.3(2.4)	0.084	0.7(1.7)	0.6(1.6)	0.862
EORTC QLQ-C30						
Global health status	80.5(21.7)	78.2(14.2)	0.632	80.0(20.3)	77.5(13.1)	0.702
Functional scales						
Physical functioning	91.0(11.3)	92.2(9.8)	0.637	91.8(10.7)	88.7(11.8)	0.392
Role functioning	94.2(13.3)	91.3(15.3)	0.390	92.6(146)	98.3(5.3)	0.840
Emotional functioning	72.7(20.9)	66.7(22.8)	0.251	72.1(21.3)	61.7(22.3)	0.154
Cognitive functioning	88.2(15.9)	83.3(15.6)	0.202	87.1(16.0)	83.3(15.7)	0.488
Social functioning	92.1(17.3)	90.4(12.7)	0.648	92.3(16.1)	86.7(13.1)	0.299
Symptom scales						
Fatigue	15.2(19.5)	18.7(22.2)	0.487	15.5(20.0)	22.2(22.8)	0.327
Nausea	6.7(19.4)	4.7(9.0)	0.625	6.4(17.8)	3.3(7.0)	0.589
Pain	6.6(14.6)	12.7(18.2)	0.119	8.3(15.7)	10.0(17.9)	0.759
Dyspnoea	5.5(14.0)	6.9(13.8)	0.664	5.8(14.0)	6.7(14.1)	0.854
Insomnia	23.0(28.6)	28.0(28.3)	0.472	22.9(28.1)	36.7(29.2)	0.152
Appetite loss	7.9(16.9)	14.7(21.7)	0.133	9.0(17.9)	16.7(23.6)	0.230
Constipation	6.1(18.2)	1.2(6.5)	0.200	4.7(16.2)	3.3(10.5)	0.798
Diarrhea	4.8(14.9)	5.1(12.3)	0.934	5.1(14.5)	3.3(10.5)	0.702
Financial problems	1.8(7.6)	0.0(0.0)	0.230	1.4(6.8)	0.0(0.0)	0.514
QLQ-BR23 Symptom scale						
Side effects	7.5(9.1)	9.9(10.3)	0.303	8.2(9.8)	8.5(7.4)	0.941
Breast symptoms	11.4(14.6)	15.0(17.8)	0.384	12.1(15.6)	15.0(17.0)	0.600
Arm symptoms	4.1(10.0)	8.0(12.6)	0.143	5.5(11.0)	4.4(10.7)	0.783
Hair loss	16.7(19.2)	20.0(29.8)	0.853	19.0(26.2)	16.7(23.6)	0.912
QLQ-BR23 Functional scale						
Body image	95.4(11.1)	88.0(19.8)	0.107	94.7(12.7)	81.5(21.6)	0.107
Sexual functioning	19.9(18.6)	20.3(23.5)	0.934	21.1(19.9)	13.3(21.9)	0.262
Future	58.0(27.6)	51.4(27.8)	0.331	56.9(28.2)	50.0(23.6)	0.467
Sexual satisfaction	57.1(18.7)	57.6(26.2)	0.957	57.8(21.3)	50.0(23.6)	0.622

Abbreviations: PBS, Phantom breast sensations; PBP, Phantom breast pain; p, significance of the differences in means (independent t-test) after Bonferoni-Holm correction.

Discussion

Prevalence of PB sensations on a group level after mastectomy remains relatively stable over time but within patients, PB sensations may disappear and reappear. This finding is in contrast with those of previous authors who found an increase over time.[9,10] Cross-sectional studies suggest a fading away with time of PB sensations based upon the observation that patients with a short follow-up report more often PB sensations than patients with a longer follow-up. However, our prospective observations did not confirm this suggestion. Remarkably some patients in our study experienced the PB sensations for the first time in the period between 26 weeks and 2 years follow-up (Table 2). This pattern of occurrence of PB sensations confirms the findings of a previous study.[34] For comparison of prevalence over time the prospective studies are summarized in figure 1.

Figuur 1. Prevalences of phantom sensations after mastectomy in prospective studies



Prevalence of PB pain reduced over a two year period of time from 7% to 1%. This reduction is in contrast with the findings of Krøner et al. who found an increase in PB pain after 6 years.[9,10] Looking at the percentages of PB pain in other studies, our prevalence is considerably lower (Table 1). This difference in prevalence might be explained by our research design. Many authors performed a cross-sectional study in which patients were asked whether they had ever experienced PB sensations or PB

pain, currently or in the past. In fact these authors assessed a period prevalence. When the period, over which is assessed, is longer in general the period prevalence also increases because every incident is included even if it has occurred only once 20 years ago. To illustrate this phenomenon, in our study the 2-year-period-prevalence is considerably higher than the prevalence at 2 years for PB sensations as well as for PB pain, 36% and 13% respectively (Table 2).

Overall, patients were only bothered to a very limited extent by PB sensations or PB pain, confirming that PB sensations or PB pain play a minor role in the lives of patients after mastectomy. During the filling out of the questionnaire patients who experienced PB sensations or PB pain explicitly told the interviewer that these sensations were not an issue in their lives. Also in previous studies little distress reported as a result of PB sensations.[11,20] For lower and upper limb amputees the percentages of subjects who were substantially bothered by phantom limb sensations or phantom limb pain are considerably higher. In lower limb amputees 23% reported to be impeded (much or very much) by phantom limb pain.[42] In upper limb amputees 41% reported to be suffering (much or very much) from phantom limb pain and 21% reported to be troubled by phantom limb sensation.[40]

Potential risk factors were analyzed for the group who experienced PB sensations any time during the 2 year follow-up and for the group who experienced PB pain any time during year follow-up. No risk factors were identified for PB sensations. Pain prior to mastectomy was not related to PB sensations or PB pain.

In conclusion, PB sensations after mastectomy occur in about a fifth of the patients and PB pain decreases over time after mastectomy. PB sensations and PB pain are of little clinical relevance in the 2 years following mastectomy.

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CHAPTER 6B

Phantom breast sensations and phantom breast pain
Part 2
A methodological analysis

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Submitted

Abstract

Aim of this study was to analyze the influence of research methodology on prevalences of phantom breast sensations (PB sensations) and phantom breast pain (PB pain).

Research design, assessment method and publication date were recorded. Data were weighted according to number of women investigated. Linear regression analysis was performed to analyze influences of methodology on prevalence of PB sensations and PB pain.

Of the 29 studies identified, 23 were cross-sectional and 6 were prospective. In 17 studies patients were interviewed and in 12 studies a questionnaire was used.

A prospective design resulted in prevalences of PB sensations and PB pain averagely 8% lower respectively 9% higher than in cross-sectional studies. Use of an interview resulted in prevalences of PB sensations and PB pain averagely 13% lower respectively 5% lower than questionnaire use. Prevalences of PB sensations and PB pain reduce averagely with 0.08% respectively 0.13% per year since 1950.

Introduction

After mastectomy, patients may experience sensory disturbances in the absent breast known as phantom breast sensations (PB sensations) and phantom breast pain (PB pain).[1,2] Papers concerning PB sensations and PB pain after mastectomy report different prevalences, ranging from 3% to 66% for PB sensations and from 3% to 53% for PB pain (figures 1 and 2).[1-31] Looking at the 95% confidence interval of the prevalence, it can be seen that the confidence intervals of many studies do not overlap, indicating significant differences in prevalences found. Possible reasons for these differences in outcomes are method of assessment, questionnaire or interview, and study design, cross sectional or prospective. Further the study populations differed between the studies, inpatients just being operated, outpatients coming for regular appointment, a mixture of these groups, or volunteers for help groups of cancer patients ("Reach to Recover" or "Women for Women"). Finally the age of population studied and the time interval between surgery and the investigation in to PB sensations varies considerably.

The aim of this study is analyze the influence of research methodology on the outcome of previously published prevalences of PB sensations and PB pain.

Material and methods

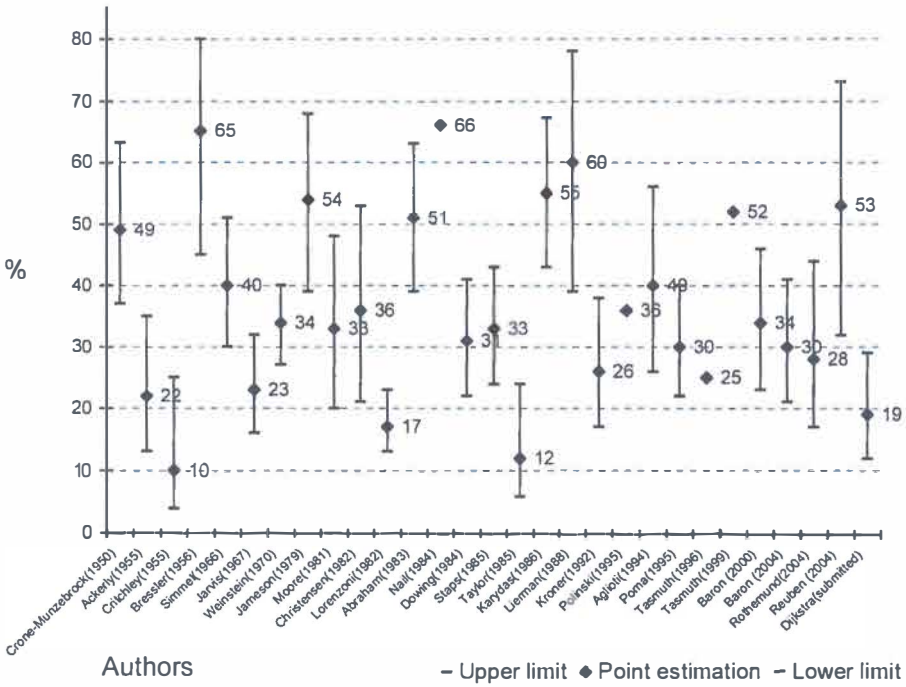
In Medline (time period 1966- 2004) publications were searched with "phantom" as free text word, combined with the term "or" with the data base specific term for phantom found in the thesaurus. Additionally in "mastectomy" as free text word, combined with the term "or" with the data base specific term for mastectomy found in the thesaurus. These two searches were combined per data base using the term "and". Papers were considered relevant for this review if they described research in which the prevalence/ incidence of phantom breast sensation/pain was investigated in patients after mastectomy. Excluded were reviews, expert opinions, case-studies as well as papers not dealing with PB sensations or PB pain. The papers identified were checked for relevant papers in the reference lists. The papers identified were read and the following items were assessed by the first author (PUD);

year of publication,
population from which the sample was selected (inpatients, outpatients or other),
age of the populations studied,
study design (cross sectional or prospective)
method of assessment (interview or questionnaire)
interval (time between mastectomy and research or in case of a prospective study the duration of the study)

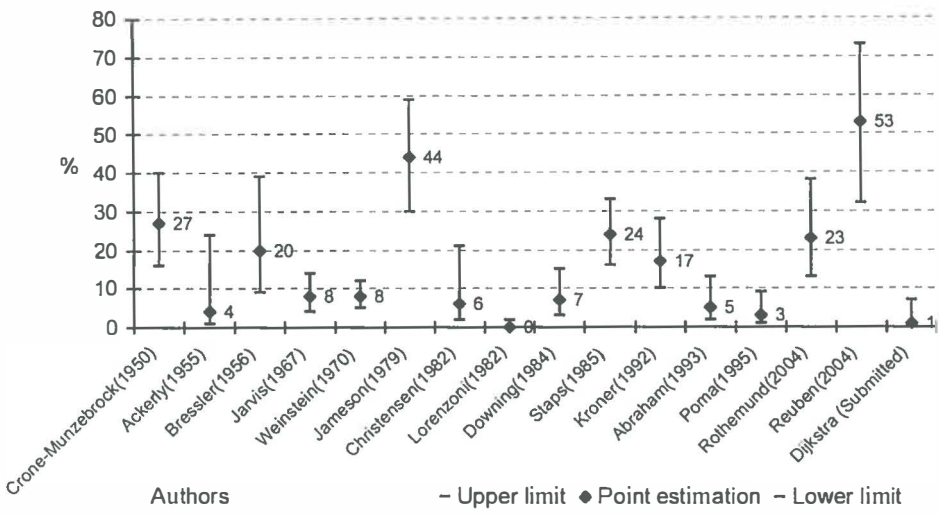
number of patients investigated
number of patients reporting PB sensations
number of patients reporting PB pain

The results of this assessment were entered in a database. Some papers described the same cohort at different follow-ups. The paper describing the longest follow-up of that cohort was entered in the data base. Data were weighted according to the number patients assessed in the study. By means of a linear regression analyses it was analyzed whether the prevalences found in literature (response variable) were related to, the time passed since publication, study design and method of assessment (predictor variables).

Figuur 1. *Prevalence and 95 % confidence intervals of phantom sensations after mastectomy*



Figuur 2. *Prevalence and 95 % confidence intervals of phantom pain after mastectomy*



Results

In total 29 studies were identified of which 23 were cross sectional and 6 were prospective. In 17 studies patients were interviewed and in 12 studies a questionnaire was used. In 25 studies PB sensations was investigated and in 17 studies PB pain was investigated (Table 1). In total 2052 women were assessed for PB sensations and 1293 women were assessed for PB pain. The weighted mean prevalence for PB sensations was 36.5% (range 10% –66%). For PB pain the weighted mean prevalence was 10.9% (range 0%-53%).

In studies with a prospective design prevalence of PB sensations was averagely 8% lower and prevalence of PB pain was averagely 9% higher than in cross sectional studies. In studies using an interview prevalence of PB sensations and PB pain was averagely 13% lower respectively 5% lower compared to studies using a questionnaire. The prevalences of PB sensations and PB pain reduce averagely with 0.08% respectively 0.13% per year since 1950 (Table 2).

Table 1. Overview of the papers published concerning phantom breast sensations and phantom breast pain

Author	Publication year	Population	Age (yrs)	Design	Method	Interval	% PBS	% PBP
Crone- Münzebrock[11]	1950	in & out patients	-	c	q	few days to > 5 yrs	49	27
Ackerly[12]	1955	-	30 - 66	c	i	7 months to 9 yrs	22	4
Critchley[13]	1955	-	-	c	i	-	10	-
Bressler[14]	1956	in & out patients	-	c	i	few days to 15 yrs	64	20
Simmel[15]	1966	in & out patients	28 - 81	c	i	4 days to 18 yrs	40	-
Jarvis[16]	1967	out patients	27 - 86	c	q	-	23	8
Weinstein[17]	1970	in & out patients	21 - 87 $	c	i	1 day to 33 yrs	33	8
Jamison[18]	1979	W for W and ACS #	32 - 70	c	q	median 10 months	54	44
Moore[20]	1981	-	-	c	i	-	33	-
Christensen[19]	1982	out patients	≤45	c	i	6 to 21 months	35	6
Lorenzoni[33]	1982	-	-	c	i	-	17	0
Abraham[21]	1983	out patients	26 - 80	c	i	3 months to 17 yrs	51	5
Nail[23]	1984	-	31 - 86	c	q	1 to 25 yrs	66	-
Downing[22]	1984	out patients	33 - 97	c	i	mean 2.6 yrs (sd:2.2)$$	30	7
Staps[24]	1985	out patients	33 - 89	c	q	mean 5.3 yrs	33	24
Taylor[25]	1985	private oncology practice out patients	29 - 78	c	i	2 to 60 months	12	-
Karydas[26]	1986	out paticnts	52.6(sd 1.3)	c	q	1 to 36 months	55	-
Lierman[27]	1988	R to R##	63.6 (sd 7)	p	i	1 to 12 months	60	-
Krøner[10]	1992	out patients	54, IQR 45 - 62	p	i	6 yrs	26	17
Polinsky[29]	1994	R to R of 5 ACS Units ###	31 - 76	c	q	1.3 to 32 yrs	36	-
Aglioti[28]	1994	in & out patients*	35 - 78	c	i	2 days to 12 yrs	40	-
Poma[30]	1996	out patients	30 - 89	c	q	2 to 16 yrs	30	3
Tasmuth[32]	1996	out patients	29 - 85	p	i	1 year	25	-
Tasmuth[31]	1999	out patients	< 70	c	q	1 year	52	-
Baron[35]	2000	out patients	25 - 82	c	q	<1month	34	-
Baron[34]	2004	out patients	>18	p	q	2 yrs	30	-
Rothemund[36]	2004	out patients	55(sd 11.6)	c	i	8 months to 25 yrs	28	23
Reuben[37]	2004	out patients**	>18	p	i	6 months	-	53
Dijkstra (current study)	-	out patients	55.6 (sd 12.8)	p	q	2 yrs	19	1

Abbreviations: Population: population from which patients were recruited , Age: age range to which the research sample was restricted , Design: study design, Method: assessment method, Interval: Interval between surgery and investigation in cross sectional studies and in prospective studies the interval over which the study was performed, PBS: phantom breast sensations, PBP: phantom breast pain, c: cross sectional study, p: prospective study, q: questionnaire, i: interview #: Half of the patients came from Women for Women self help recovery group and the other half cam from the American Cancer Society , ##: Patients were recruited from the Reach to Recovery program of the American Cancer Society Units, ###: Patients were recruited from the Reach to Recovery volunteers of five American Cancer Society Units, -: not reported /not investigated, *: subjects who received quandrantectomy were excluded, **: The subjects were patients receiving a mastectomy in a control group of a RCT, $: at the time of mastectomy, $$: pooled data , IQR: Interquartile range. Of the prospective studies the last recorded prevalence is entered in the table.

Table 2. Influence of study design, method of assessment and the time passed since publication on the prevalence's of PB sensations and PB pain

Response variable	Predictor variables	ß	95% CI ß	Explained variance
Phantom breast sensations				19.3%
	interview (yes=1, no=0)	-13.0	-14.3 to -11.8	
	prospective study (yes=1, no=0)	-8.2	-10.6 to -5.8	
	years after 1950 (per year)	-0.08	-0.13 to -0.03	
	constant	46.2	44.2 to 48.3	
Phantom breast pain				10.4%
	interview (yes=1, no=0)	-5.2	-6.4 to -4.0	
	prospective study (yes=1, no=0)	9.4	7.5 to 11.3	
	years after 1950 (per year)	-0.13	-0.18 to -0.08	
	constant	16.8	15.1 to 18.6	

Abbreviations: CI: confidence interval

Discussion

Research design, prospective or cross-sectional significantly influenced the outcome of prevalences of PB sensations and PB pain. Cross-sectional studies produce higher prevalences for PB sensations and lower prevalences for PB pain compared to prospective studies. The assessment method has also a strong influence on the outcome of the prevalences of PB sensations and PB pain. A questionnaire overestimates the prevalences compared to an interview. A very small but significant influence of time was found. The prevalences found of older studies are higher than the prevalences in more recent studies.

In the search for an explanation of differences in prevalences the above mentioned variables only contribute to a limited extend, looking at the explained variance of the regression analyses. Other variables influencing the estimation of prevalences could not be analyzed because these variables were described sketchily in a substantial amount of studies. For instance the population (inpatients or outpatients) from which the study sample was drawn was not described in 5 studies. In some studies the study population was drawn from a Reach for Recovery Group of the American Cancer Society or a Women for Women Self Help Group. It is quite probable that these groups are more aware of PB sensations and PB pain because of their participation in these groups. Further the circumstances of the assessments differed considerably. In some studies patients were assessed during psychological treatment while in other studies patients were assessed during standard follow-up or the investigator visited the women at home. In different studies it was found that patients amputated at a younger

age more often experience PB sensations than patients amputated at an older age. This difference in experiencing PB sensations is possibly related to the menstrual cycle.[3,4,9,10] Thus age is a potential risk factor for PB sensations. However, age of the study population was described inadequately in many studies. Age ranges were generally described, and sometimes completed with the mean age (Table 1). Seldom were mean and standard deviation provided or median and interquartile ranges.

Similarly time interval between mastectomy and research was seldom described adequately, despite that this interval is a factor associated with PB sensations and PB pain because of the fading away phenomenon. Looking at the ranges of these intervals it is clear that the interval between mastectomy and research differs between the studies. As a consequence prevalences of PB sensations and PB pain reported in literature reflect period-prevalences over different periods of time. It can be hypothesized that the longer the period between mastectomy and investigation, the higher the prevalence might be.

In some studies, patients with a lumpectomy were assessed for PB sensations or PB pain. In our analysis for the estimation of the overall prevalence we excluded these patients because we felt that patients with a lumpectomy can hardly be expected to differentiate between that part of the breast still present and the amputated part.
Finally some studies only provided percentages of patients suffering from PB sensations and PB pain without describing the actual number of patients suffering from it.

Despite these shortcomings in PB sensations and PB pain research, three variables were significantly related to the prevalences found; design of the research, method of assessment and years since 1950.

The discrepancy that cross-sectional studies result in a higher prevalence of PB sensations and a lower prevalence of PB pain compared to prospective studies cannot be explained satisfactorily. It can be hypothesized that in cross sectional studies the prevalence might be over-estimation especially if the patient is asked if she had experienced PB sensations or PB pain any time in the past. But why this mechanism might result in a different outcome for PB sensations and PB pain is not clear.

Consequences of the use of a questionnaire might be that patients do feel safe to answer the questions about sensations that are hard to understand. Additionally patients may confuse sensations of differentiation or cicatrical pain with PB sensations and PB pain and incorrectly report to be suffering from PB sensations of PB pain. Consequences of an interview might be that the interviewer unwillingly introduces bias on the basis of his own hypothesis about the prevalence or the patients do not feel free to report PB sensations or PB pain. An advantage of an interview is that the interviewer can explain what type of sensations and pain is actually meant by PB sensations and PB pain.

The reduction of the prevalence over time might be explained by less extensive surgery for breast cancer treatment in recent years. In the fifties and the sixties the

major pectoralis muscle was resected also together with the affected breast.[3] Today surgery does not involve the major pectoralis muscle anymore unless ingrowths of the tumor makes it necessary.[32,33]

A consequence of the outcome of this analysis is that an assessment instrument should be developed which is valid, reliable and responsive. Recently a questionnaire was developed to assess 18 sensations in arm and chest region after breast cancer treatment. [26] This questionnaire was assessed for its psychometric properties and was found to be reliable and valid. To that questionnaire one item was added to assess PB sensations. However, that specific item was not included in the psychometric analysis thus leaving researchers still with empty hands.

In conclusion research design, assessment method, and time have a significant effect on prevalences of PB sensations and PB pain reported in literature.

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CHAPTER 7

Validity and intra- and interobserver reliability of indirect volume measurements in patients with upper extremity lymphedema

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Published
Lymphology 2004;37(3):127-34

Abstract

We investigated a method of indirect volume measurement that utilized surface measurements and a simplified formula derived from the formula for a frustum (Sitzia's method) to determine limb volumes in patients with breast cancer-related lymphedema of the upper extremity.

Repeated measurements of upper-extremity limb volume were obtained by two observers on both upper extremities of 30 women with unilateral lymphedema. Volume was calculated using a simplified formula and compared with water displacement method as a gold standard.

Indirect volume determination using Sitzia's method is comparable with the water displacement method, has comparable intra- and interobserver reliabilities, and can be used for diagnosis and follow up measurements of lymphedema. Indirect volume determination using surface measurements at 8 cm intervals is only suitable for follow up measurements. The methods should not be used interchangeably.

Introduction

The incidence of breast cancer in The Netherlands is 127/100,000 woman per year.[1] Lymphedema of the upper extremity is a common complication of breast cancer treatment. The reported prevalence of arm edema as a result of breast cancer treatment ranges from 6 to 43%.[2] Lymphedema is an accumulation of lymph fluid in the limb resulting from an insufficiency of the lymphatic system.[3] Quoted prevalence rates for lymphedema after breast cancer treatment vary.[2] This variation in prevalence may be attributed to different assessment methods, levels of awareness of the problem and lack of an universally accepted definition of which degree of swelling defines "lymphedema".[2,4-7] Patients can develop an uncomfortable, unsightly and sometimes functionally impaired limb prone to repeated episodes of superficial infections.[4-9]

As improved methods for the assessment and treatment of edema related problems are developed, the need for reliable outcome indicators also increases.[8] The volume of the upper extremity is measured directly or indirectly calculated using measurements and a mathematical formula. The "gold standard" is defined as the volume determined by water displacement, although not all authors share this opinion.[10-12] This method, however, has some disadvantages in that it is laborious and difficult to use in a clinical setting because of the difficulties in filling the volumeter and the risk of spilling water, and it gives no insight into which part of the upper extremity is swollen.

Besides the water displacement method, other indirect methods to assess lymphedema include circumference measurements, surface measurements, optoelectronic measurements, computer tomography and magnetic resonance imaging.[5-8,13,17,18]

Casley-Smith has reported a very good correlation between simultaneous measurements of edema of the upper extremity by water displacement and by calculating volumes from circumferences.[19] Nevertheless, intra- and interobserver reliability were not assessed. A similar study has been done for the lower extremities, but it used a population without edema.[11] Karges et al. concluded that calculated volume measurements, determined by summing segment volumes derived from truncated cone formula, were highly associated with measures based on water displacement but that the measures were not interchangeable.[20] Sander et al found that, although volume of an edematous upper extremity calculated by geometric formulas correlated strongly with the volume determined by the water displacement, the measures obtained by the two methods did not agree.[21] Similar results were found by Megens et al. in women at risk for edema following axillary lymph node dissection surgery for breast cancer.[22]

Sitzia describes a method (in this manuscript called: Sitzia's method) that uses surface circumference measurements (at 4 cm intervals) and a mathematical formula, derived from a formula for a frustum, to determine the volume of the upper

extremity.[9] This method is cheap, relatively easy, feasible, and hardly bothersome to the patient. Furthermore, volume can be calculated for different segments of the upper extremity and an indication can be given of the distribution of lymph fluid.

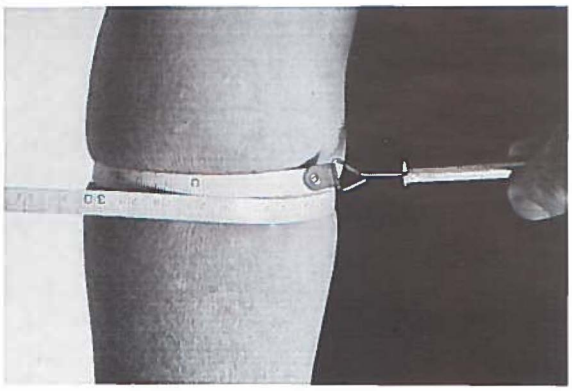
The aim of this study was to investigate the intra- and interobserver reliability as well as to compare volume determination using indirect volume determination (Sitzia's method) and water displacement method.

Patients and methods

The study group consisted of 30 patients 18 years and older (mean 56.4 ± 11.6 S.D.) with breast cancer treatment related upper limb lymphedema (18 right and 12 left upper extremities). Exclusion criteria for this study were co-morbidity (such as serious kidney, heart- and lung disorders, skin damage/infections in the upper extremities), recent operation on the upper extremity, the inability to elevate the upper extremity 90 degrees in the shoulder girdle, or the inability to extend the elbow. Signed consent was obtained from all volunteers in the study and the study was approved by the Medical Ethical committee of the University Hospital Groningen.

Assessments were performed by two observers using a commercially available measuring apparatus which practitioners can easily acquire and are frequently used in daily clinical practice. Circumference was measured on both arms at 4 cm intervals using a special designed tape measure with holes at every 4 cm. Using a surgical marking pen (standard line VX100, Cory Bros), dots were made on both upper extremities. The first dot was on the styloid process of the radial bone. At each dot the circumference was determined using a Gulick Measuring Tape® (Lafayette Instruments; model 258-J00305, Lafayette, Indiana, USA), by which the amount of tension during measurement can be standardized (Figure 1).

Figure 1. *Gulick Measuring Tape*



Furthermore, we compared the accuracy of the indirect method using circumference measurements at 8 cm intervals. The volume of the upper extremity is calculated[9] using the following formula described by Sitzia where c stands for the circumference of the arm every 4 or 8 cm (L).

$$V = \frac{L}{4\pi} (c1c2 + c2c3 + c3c4 + \ldots\ldots + c13c14)$$

After obtaining these measurements, both upper extremities were independently immersed in a water displacement volumeter (Sammons-Preston®, Model 258-F00605, 7"x7"x30"), which was filled with water with a pleasant temperature of approximately 25°C. The water displaced by the hand (to the first dot on the styloid process) was collected separately. Then the arm was put into the volumeter until the front armpit line touched the edge of the volumeter. Care was taken to ensure the upper extremity was placed perpendicularly into the water and displaced. Water was collected in measuring cups with a 10 cc calibration. Both arms were patted dry at the end of the measuring session, and the dots were removed by means of stirilium disinfection lotion. The assessment was performed three times. The first and third measurements were performed by one observer and the second assessment by the second observer, hence intra- and inter observer variation could be determined. Observer sequence was determined randomly.

Statistical analysis included the T-test (paired samples statistics) and intra class correlation (one-way random) (SPSS 10.0).

Results

Both the intra- and inter observer reliability of the water displacement method and Sitzia's method using surface measurements with 4 and 8 cm intervals showed no significant differences for both the affected and unaffected upper extremity (Tables 1-3).

Volume determination using Sitzia's method with 8 cm interval surface measurements in comparison with the water displacement measurements produced a significant difference (mean difference of 187 ml [±380.4 SD, p=0.01] for observer 1 and 193 ml [± 337 SD, p<0.01] for observer 2 [Table 4]). Four cm interval circumference measurements in comparison to the water displacement method showed no significant differences (mean difference of 31.6 ml [± 280.9 SD, p=0.54] for observer 1 and 22.9 ml [± 297.5 SD, p=0.68] for observer 2 [Table 4]).

Significant difference was found comparing the mean volume difference of the affected upper extremity using Sitzia's method with surface measurements at 4 cm intervals to those using 8 cm intervals (mean difference of 219.5 ml [± 206 ml SD, p=<0.01] for observer 1 and 215.9 ml [± 217.2 SD, p<0.01] for observer 2 [Table 5]).

Table 1 Intra observer reliability of the water displacement method (15 paired observations). Volume expressed in ml

	Mean 1 (SD)	Mean 2 (SD)	Mean difference (SD)	95% CI of mean difference	Sig. (2-tailed)	Intra class correlation
Observer 1						
Affected arm.	2563.3 (535.9)	2616 (555)	52.7 (105.7)	-111.2 to 5.9	0.07	0.98
Unaffected arm.	2182 (461.2)	2236 (471.3)	54 (142.2)	-132.8 to 24.8	0.16	0.95
Observer 2						
Affected arm.	2907.3 (644.2)	2896 (635.4)	11.3 (148.5)	-70.8 to 93.5	0.77	0.97
Unaffected arm.	2362.3 (547)	2326.3 (509.4)	36 (146.6)	-45.2 to 117.2	0.36	0.96

Abbreviations: ml; milliliters, SD; standard deviation, CI; confidence interval, Sig; significance

Table 2. Intra observer reliability of Sitzia's method. Surface measurements at 4 cm. and 8 cm. intervals (15 paired observations). Volume expressed in ml

	Mean 1 (SD)	Mean 2 (SD)	Mean difference (SD)	95% CI of mean difference	Sig. (2-tailed)	Intra class correlation
Observer 1						
4 cm. intervals. Affected arm.	2537.2 (453.5)	2551.1 (475)	13.9 (55.6)	-44.7 to 16.9	0.35	0.99
4 cm. intervals. Unaffected arm.	2210 (400.4)	2232.2 (448.8)	22.2 (115)	-85.9 to 41.5	0.47	0.96
8 cm. intervals. Affected arm.	2353 (442.3)	2362.2 (459.6)	9.2 (54.5)	-39.4 to 21	0.53	0.99
8 cm intervals. Unaffected arm.	2034.9 (396.6)	2067.4 (441.5)	23.6 (177.9)	-122.1 to 75.0	0.62	0.91
Observer 2						
4 cm intervals. Affected arm.	2925.1 (619.6)	2939.1 (601)	14 (180.3)	-113.9 to 85.9	0.77	0.96
4 cm intervals. Unaffected arm.	2374.9 (426.5)	2422.5 (480.1)	47.6 (201.7)	-159.3 to 64.1	0.38	0.9
8 cm intervals. Affected arm.	2723.7 (705.3)	2782.7 (624)	59 (260.6)	-203.3 to 85.3	0.40	0.92
8 cm intervals. Unaffected arm.	2130.9 (379)	2255.7 (460.9)	124.8 (359.2)	-323.7 to 74.1	0.20	0.62

Abbreviations: ml; milliliters, SD; standard deviation, CI; confidence interval, Sig; significance

Table 3. Inter observer reliability of the water displacement method and Sitzia's method, using surface measurements at intervals of 4 cm. and 8 cm. (30 paired observations). Volume expressed in ml

	Mean 1 (SD) Observer 1	Mean 2 (SD) Observer 2	Mean difference (SD)	95% CI of mean difference	Sig. (2-tailed)	Intra class correlation
Water displacement. Affected arm.	2698.3 (606)	2749.6 (570.1)	51.3 (249.2)	-144.3 to 41.8	0.30	0.91
Water displacement. Unaffected arm.	2240.3 (470.6)	2268 (467.3)	45.7 (178.8)	-112.4 to 21.1	0.17	0.92
Sitzia's method (4 cm intervals). Affected arm.	2729.9 (466.9)	2772.5 (553.9)	42.6 (259.5)	-138.4 to 53.2	0.37	0.88
Sitzia's method (4 cm intervals). Unaffected arm.	2314.4 (391.4)	2330.2 (436.6)	15.9 (233)	-102.9 to 71.1	0.71	0.85
Sitzia's method (8 cm intervals). Affected arm.	2510.4 (463.5)	2556.6 (613)	46.2 (404.9)	-197.4 to 104	0.54	0.73
Sitzia's method (8 cm intervals). Unaffected arm.	2129.7 (399.7)	2105 (415.1)	24.6 (310.2)	-91.2 to 140.5	0.67	0.72

Abbreviations: ml; milliliters, SD; standard deviation, CI; confidence interval, Sig; significance

Table 4. Sitzia's method, using surface measurements at 4 cm. and 8 cm. intervals, versus water displacement method (affected arm, 30 paired observations). Volume expressed in ml.

	Mean 1 (SD) Sitzia's method	Mean 2 (SD) Water displacement	Mean difference (SD)	95% CI of mean difference	Sig. (2-tailed)	Intra class correlation
4 cm. intervals. Observer 1.	2729.9 (466.9)	2698.3 (606)	31.6 (280.9)	-73.3 to136.5	0.54	0.87
4 cm intervals. Observer 2.	2772.5 (553.9)	2749.6 (570.1)	22.9 (297.5)	-88.2 to 134	0.68	0.86
8 cm. intervals. Observer 1.	2510.4 (463.5)	2698.3 (606)	187 (380.4)	-330 to -46	0.01	0.71
8 cm intervals. Observer 2	2556.6 (613)	2749.6 (570.1)	193 (337)	-318.8 to -67.2	0.00	0.8

Abbreviations: ml; milliliters, SD; standard deviation, CI; confidence interval, Sig; significance

Table 5. Sitzia's method, using surface measurements at 4 cm. intervals, versus surface measurements at 8 cm. intervals (affected arm, 15 paired observations). Volume expressed in ml

	Mean 1 (SD) 4 cm. intervals.	Mean 2 (SD) 8 cm. intervals	Mean difference (SD)	95% CI of mean difference	Sig. (2-tailed)	Intra class correlation
Observer 1.	2729.9 (466.9)	2510.4 (463.5)	219.5 (206)	142.6 to 296.4	0.00	0.8
Observer 2.	2772.5 (553.9)	2556.6 (613)	215.9 (217.2)	134.8 to 297	0.00	0.92

Abbreviations: ml; milliliters, SD; standard deviation, CI; confidence interval, Sig; significance

Discussion

Intra- and inter observer reliability of the water displacement method and Sitzia's method were both good. These results are comparable with the results of other researchers who have performed similar assessments.[20-22] Further, a strong correlation (no significant difference) between Sitzia's method using surface measurements at 4 cm intervals and the water displacement method was found.

Although the intra observer reliability showed no significant mean difference, the standard deviation of the mean difference was relative large in both the water displacement method and Sitzia's method. This especially applies to the results of observer 2 using Sitzia's method to calculate the volume with 8 cm interval surface measurements (affected arm: mean 59 ml [± 260.6 S.D.], unaffected arm: mean 124.8 ml [± 359.2 S.D.]). In only one comparison, the intra class correlation was not acceptable (0.62) (Table 2).

Segerström et al [23] has defined edema of the arm as a volume difference of 150 ml, and using this criterion, both methods are not accurate enough to assess this difference reliably. Water displacement and surface measurements are now the most used methods for upper extremity volume determination, and possibly this definition of arm edema may necessitate changing the volume difference to a higher limit. Noteworthy is the fact that volume determination using Sitzia's method with 4 cm interval measurements and the water displacement method are reasonably correlated.

If Sitzia's method using 4 cm and 8 cm interval surface measurements is compared to water displacement, a relatively large standard deviation in the mean difference is found (Table 4), suggesting that the measures should not be used interchangeably, as has been concluded previously.[20-22] Although volume determination using 8 cm interval has a poor correlation with the water displacement method (Table 4) and the

inter observer reliability is poor (Table 3), the intra observer reliability is quite good (with the one exception mentioned). This could imply that follow up measurements using 8 cm interval surface measurements can be used, although the observers are not interchangeable. The latter method should gain some time in daily clinical practice.

In view of the large standard deviation in both the intra observer reliability of observer 1 and 2 and the inter observer reliability it can be questioned if the water displacement method should be regarded as the "gold standard." The theoretical principles of the direct volume determination are without question correct but in practice it does not always allow precisely accurate measurements. Though upper extremity volume determination using the indirect volume determination with circumference intervals of 4 cm can be performed reasonably fast and easily, a drawback of this method is that the volume of the hand can not be determined by this method. Because many patients with edema of the upper extremity have impairments due to the fact that they have hand edema, determination of the hand volume should be done using the water displacement method.

In conclusion regarding clinical implications: indirect volume determination using surface measurements with 4 cm intervals with a formula for a frustum (Sitzia's method) is comparable with the water displacement method ("the gold standard"), with comparable intra- and interobserver reliabilities. Sitzia's method can be used in diagnosis and follow up measurements of lymphedema. Indirect volume measurements using surface measurements with 8 cm intervals are only suitable for follow up measurements, and the methods should not be used interchangeably.

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CHAPTER 8

Long-term treatment related upper limb morbidity, daily activities and quality of life after sentinel lymph node biopsy or axillary lymph node dissection for stage I or II breast cancer

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Abstract

Background

In a prospective study, long term upper-limb morbidity, perceived disabilities in activities of daily life (ADL) and quality of life (QOL) were assessed before and two years after sentinel lymph node biopsy (SLNB) or axillary lymph node dissections (ALND) for breast cancer.

Methods

204 patients with stage I/II breast cancer, mean age 55.6 years (sd: 11.6) entered the study and 181 patients (89%) could be evaluated after two years. 57 patients underwent SLNB (31%) and 124 patients underwent an ALND (69%). Assessments included pain, shoulder range of motion, muscle strength, arm volume, perceived shoulder disability in ADL and QOL.

Results

Significant ($p<0.05$) changes between before and two years after surgery were found in almost all assessments of shoulder function, ADL and several QOL subscales. Patients in the ALND group showed significant more changes in range of motion (ROM) in abduction and abduction / external rotation, grip strength, arm volume, ADL and QOL physical- and role functioning, pain and sleeplessness and arm symptoms compared to the SLNB group. Multivariate linear regression analysis showed that ALND could predict decrease of ROM in abduction, grip strength, ADL and physical functioning (QOL) and increase of arm volume, pain and arm symptoms score (QOL). Radiation on the axilla predicts an additional decrease in shoulder ROM and increase of arm volume.

Conclusion

Two years after surgery for breast cancer, patients show significantly less treatment related upper limb morbidity, perceived disability in ADL and worsening of QOL after SLNB compared with ALND.

Introduction

The aim of modern breast cancer treatment is to obtain local tumor control, optimal lymph node staging with minimal treatment related morbidity, good functional result and when possible preservation of the breast. Due to breast cancer screening programs and multimodality breast cancer treatment the number of patients cured after breast cancer is still increasing as do the 5 and 10 year survival.[1,2] As a result, impairments, disability in activities of daily life (ADL) and decrease of quality of life (QOL) induced by the multimodality breast cancer treatment are important issues to be aware of.

Axillary lymph node status based on the amount of positive axillary lymph nodes in relation to the total amount of resected lymph nodes is an important prognostic factor in patients with breast cancer.[3-5] Axillary lymph node dissection (ALND) still is associated with upper limb morbidity such as pain, numbness, lymphedema, weakness and impaired shoulder range of motion.[6] Persisting upper limb morbidity can affect the ability to perform ADL and QOL.[6-8] The impact of upper limb morbidity on disabilities in ADL and QOL in breast cancer patients has rarely been studied with modern assessment instruments.[6]

Sentinel lymph node biopsy (SLNB) was introduced for staging of the axilla to reduce the number of unnecessary ALND's.[9] SLNB is an accurate and safe procedure to predict metastatic disease in clinically negative axillary lymph nodes and is more and more accepted in breast cancer treatment.[9-11] An increasing number of studies reported less treatment related morbidity for SLNB in comparison to ALND.[12-20] A minority of these studies investigated upper limb morbidity and perceived disability in ADL after SLNB in comparison to ALND.[13,16,19] Generally disability in ADL of the SLNB group was less than that of the ALND group.[13,16,19] A shortcoming in most studies is the absence of pre-treatment assessment and the absent of reliable and validated assessment instruments. Although association between upper limb morbidity and poorer QOL was described, QOL is seldom considered in the debate on axillary surgery.[6,8,20-22]

The aim of the current prospective study was to analyze long-term upper limb morbidity, perceived disability in ADL and QOL two years after SLNB or ALND. The second aim was to analyze to which extent ALND and other treatment variables could predict upper limb morbidity, perceived disability and decreased QOL. At third, correlations between upper-limb morbidity and disability in ADL and reduction in QOL were analyzed.

Patients and methods

From June 1999 to June 2001, patients with breast carcinoma stage I or stage II entered the study.[23] Patients were retrieved from the Groningen University Medical Centre and the Martini Hospital Groningen. Informed consent was obtained from the participating patients. The protocol was approved by the Institutional Review Board of both hospitals. Two groups of breast cancer patients participated in the prospective study, patients who underwent conventional breast cancer treatment with an ALND and patients who were treated according the SLNB concept. Patients with positive sentinel lymph nodes received subsequently an ALND and were included in the ALND group.

Sentinel lymph nodes were identified by pre-operative lymphoscintigraphy followed by intra-operative tracing using a gamma probe and Patent blue dye® (Blue Patenté; Labatoire Guerbet, Aulnay-sous-Bois, France). The procedure has been previously described in detail.[24] If pathological examination revealed metastases in the sentinel lymph node, ALND was performed within two weeks after SLNB. Surgical and adjuvant treatments were applied according to the protocol of the Comprehensive Cancer Centre North-Netherlands (CCCN) in both groups (Table 1).

Upper limb function and ADL were assessed one day before surgery (t0) and two years after surgery (t1). Pain was assessed with the Visual Analogue Scale (VAS) (Table 2). The patient was asked to mark their current pain on a 10 cm straight line (0 cm = no pain, 10 cm = worst pain imaginable).[25]

Upper limb function was assessed by means of a protocollized physical examination (Table 2). Active shoulder range of motion was measured, using a goniometer (Isomed Inclinometer; Portland, Oregon, USA) according to a standardized protocol in forward flexion, abduction and external rotation.[26] Muscle strength of shoulder abductors and elbow flexors were measured using a handheld dynamometer (Citec®; Groningen, The Netherlands).[27,28] For assessment of the grip strength, a Yamar® hand-dynamometer (Bollingbrook, Ilinois, USA) was used.[29] All muscle strength measurements were performed three times and the mean of these three measurements was used for further analysis.

Arm volume was assessed by means of surface circumference measurements (at 4 cm intervals) and a mathematical formula (Sitzia's formula) derived from a formula for a frustum.[30,31] Circumferences were measured using a Gulick Measuring Tape® (Lafayette Instruments; model 258-J00305, Lafayette, Indiana, USA) at 4 cm intervals proximal from the styloid process of the ulnae.

ADL was assessed with the Shoulder Disability Questionnaire (SDQ) and the Groningen Activity Restriction Scale (GARS). The SDQ is a functional status measure that covers 16 items. It was designed to evaluate the ability to perform daily activities in patients with shoulder disorders (shoulder related ADLs).[47,48] It contains 16 statements that patients with shoulder disorders have used, to describe in what kind

of ADL situations they experience pain. It has a three-category response format; for example; 1, "Yes my shoulder is painful when I open or close a door"; 2, "No my shoulder is not painful when I open or close a door"; 3, "I did not perform the activity during the past 24 hours". The total scoring range for the 16 statements was transformed to 0-100. Score of 0 means no functional status limitation and a score of 100 means maximum functional status limitation (Table 2).[32]

The GARS assesses the perceived restrictions (disability) in performing 18 ADLs.[33,34] It has a four-category response format: 1, Able to perform the activity without any difficulty; 2, Able to perform the activity with some difficulty; 3, Able to perform the activity with much difficulty; 4, Unable to perform the activity independently. The sum scoring range is 18-72. With a score of 18 the person can perform all the activities without any difficulty; with a score of 72 the person cannot perform any activity without the help of others (Table 2).[33,34]

Table 1. Tumor-node-metastasis classification, receptor status and treatment characteristics of the patients who completed the assessments before surgery and two years after initial treatment

Variable	SLNB (n=57)	ALND (n=124)	Total (n=181)
Patient age, years, mean (SD)	57 (11.9)	55 (11.0)	56 (11.3)
Tumor-Node-Metastasis classification			
Stage I	44 (77%)	39 (32%)	83 (45%)
Stage IIA	11 (19%)	66 (53%)	77 (43%)
Stage IIB	2 (4%)	19 (15%)	21 (12%)
Estrogen-receptor status			
Positive	35 (61%)	89 (72%)	124 (68%)
Negative	22 (39%)	35 (28%)	57 (32%)
Surgical treatment of breast			
Mastectomy	17 (30%)	57 (46%)	74 (40%)
Lumpectomy	40 (70%)	67 (54%)	107 (60%)
Adjuvant therapies*			
Radiotherapy of breast	37 (65%)	79 (64%)	116 (64%)
Radiotherapy of axilla	0 (0 %)	14 (11%)	14 (8%)
Chemotherapy	9 (16%)	51 (41%)	60 (33%)
Hormonal therapy	10 (18%)	64 (52%)	74 (41%)

Abbreviations: *: patients could receive more kinds of therapies

Table 2. Assessment of shoulder function, activities of daily life (ADL) and Quality of life (QOL)

Assessment	Assessment tool
Shoulder function:	
Pain (current pain)	VAS[25] *(cm)*
Numbness	Clinical examination: numbness *yes* or *no*
Active shoulder range of motion:	Isomed® Inclinometer.[26] *(°)*
Forward flexion	
Abduction	
Combined abduction/external rotation	
External rotation	
Muscle strength:	Citec® handhold dynamometer.[27,28] *(Nm)*
Shoulder abductors	
Elbow flexors	
Grip strength (cylinder grip)	Yamar® hand-dynamometer.[29] *(Nm)*
Arm volume	
Circumference at 4 cm intervals proximal to the processus styloideus ulnae)	Gulick Measuring Tape (Lafayette Instrument; model 258-J00305) *(cm)*
	Sitzia's formula.[30,31]
ADL	SDQ[32]
	GARS[33,34]
QOL	EORTC QLQ-C30 and QLQ-BR23.[35]

Abbreviations: VAS: visual analogue scale; cm: centimeters; (°): degree; Nm: Newton meter; SDQ: The Shoulder Disability Questionnaire[32]; GARS: The Groningen Activity Restriction Scale[33,34]; EORTC QLQ: European Organization on Research and Treatment of Cancer Quality of Life Questionnaire.[35]

Quality of Life was assessed with help of the EORTC QLQ-C30 questionnaire supplemented with the EORTC Breast Module (EORTC QLQ-BR23).[35] The EORTC QLQ-C30 is a recognized and validated health related QOL questionnaire, developed by the European Organization on Research and Treatment of Cancer (EORTC) Study Group on QOL.[35] The core questionnaire is intended to measure general aspects of health related QOL specific to cancer patients. It incorporates five functional scales on physical, role, cognitive, emotional and social functioning. There are three symptom scales including fatigue, pain and nausea and vomiting. Single items are dyspnoea, insomnia (sleeplessness), loss of appetite, constipation, diarrhea, perceived financial impact and global health status. Each item is scored in one of four categories: 1, Not at all; 2, A little; 3, Quit a bit; 4, Very much, with exception of the scoring of global health status which ranges from; 1, Very poor, to 7, Excellent.[36] The supplementary EORTC Breast module is a site specific module which includes four functional scales

on body image, sexual functioning, sexual enjoyment (satisfaction), future perspective and four symptom scales/items including arm symptoms, breast symptoms, systemic-therapy side effects and upsetness by hair loss. The breast module is constructed in a similar manner like the core questionnaire (QLQ-C30). A linear transformation to a '0-100' scale of the EORTC QLQ-C30 and the QLQ-BR23 was carried out according to the EORTC Scoring Manual.[36] A higher mean score for functional scales and global QOL reflects a better level of functioning, but a higher mean score for the symptom scales/items reflects more symptoms/problems.

Statistical analyses included descriptive statistics and *t*-tests for independent samples for between-group comparisons and *t*-tests for dependent samples for within-group comparisons. Pearson's χ^2 test was used for dichotomous variables. To answer the question in which extent treatment variables could predict upper limb morbidity, perceived disability and poorer QOL, multivariate linear regression analyses were performed with the following independent variables: ALND, surgical treatment breast (modified radical mastectomy or lumpectomy), and radiation axilla and radiation breast. Differences were accepted as significant if p values were <0.05. SPSS® Base 11.5 software for Windows® ,SPSS Inc., was used for statistical analysis.

Results

In the period 1999-2001, 204 consecutive patients with invasive breast carcinoma were included in the study. Initially 124 patients (61%) underwent a SLNB. Fifty-eight patients (47%) subsequently underwent additional ALND due to metastasis in the sentinel node. Therefore the study comprised of 66 patients with SLNB (32%) and 138 patients with a level I-II ALND (68%).

Two years after surgery, twenty-three patients of the 204 patients (11%) could not be assessed. Fourteen patients belonged to the ALND group and 9 patients to the SLNB group. From the ALND group 6 patients died of metastatic disease; one patient had a breast reconstruction and was excluded from assessment, three patients withdrew from the study because of psychological burden and four patients withdrew because of other reasons. From the SLNB group one patient had distant metastasis, one patient refused further treatment and seven of them found the assessment protocol bothersome and chose to withdraw from the study. These seven patients had no upper limb complaints. 181 patients could be evaluated; 57 patients (32%) in the SLNB group and 124 patients (68%) in the ALND group. TNM classification, receptor status and treatment characteristics of these patients are presented in Table I.

After two years substantial long-term treatment-related upper-limb morbidity was observed for the whole study group. Significant changes between before surgery and two years after surgery were found in all assessments except strength of the elbow flexors (Table 3). There was a small but significant increase in self-assessed pain

perception (VAS) from 0.4 (SD 1.1) to 0.7 (SD 1.4). Numbness of the axillary region was observed in 114 patients (63%). The largest decrease in range of motion of the shoulder was found in abduction (16.2°; SD 31.0). Decrease in grip strength (33.6 Nm, SD 51.7) and muscle strength of the shoulder abductors (10.0 Nm; SD 29.9) was observed. Mean volume of the arm was increased with 124 ml (SD 241). Disability on ADL increased as assessed with the SDQ (10.5; SD 29.9) and the GARS (1.8; SD 5.7) (Table 3).

Also significant changes were found for QOL assessed with the EORTC QLQ-C30 and QLQ-BR23. Physical and role functions decreased. Emotional function and symptom scales/items such as fatigue, pain, dyspnoea, constipation and financial problems increased. From the functional scales of the breast cancer module, body image decreased (-3.2 SD 17.1) while future perspective increased (12.7 SD 28.2). Also here was an increase of side effects (4.8 SD 13.2) and arm symptoms (8.8 SD 19.4) (Table 4).

Several changes in upper-limb function (upper-limb morbidity), ADL (perceived disability) and QOL between before surgery and two years after treatment were significantly different between the SLNB group and the ALND group in favor of the first (Tables 5 and 6).

No significant difference was found for the change in pain perception of both groups (Table 5). Numbness was still observed two years after surgery in 10 patients in the SLNB group (18%) and in 104 patients of the ALND group (84%) ($p<.0001$ χ^2 test). Considering ROM of the shoulder, the largest difference was found in shoulder abduction (15.5°; 95% confidence interval [95% CI]: 7.4 to 23.7) (Table 5). No significant difference was found in the forward flexion and external rotation between the groups. Considerable significant differences were observed for grip strength (24.1 Nm; 95% CI: 8.0 to 40.3) but not for strength of shoulder abductors and elbow flexors (Table 5). The difference of mean change in arm volume between SLNB and ALND are significant (184 ml; 95% CI: 124 to 243) (Table 5). Considering the increase in perceived disability in ADL, significant difference between the SLNB group and the ALND group was found for the GARS (2.3; 95% CI: .9 to 3.8) but not for the SDQ (8.4; 95% CI: -.1 to 16.9) (Table 5).

Differences in QOL changes between the SLNB group and ALND group were significant for physical functioning (6.4; 95% CI: 2.6 to 10.1), role functioning (7.5; CI: .3 to 14.7), pain (8.1; CI: 1.8 to 14.4), insomnia (sleeplessness) (10.5; CI: 1.2 to 19.8) and arm symptoms (8.5; CI: 3.6 to 13.4) (Table 6).

Multivariate linear regression analysis to predict the mean change in upper-limb function, ADL and QOL between before treatment and two years after treatment for independent variables age, axillary surgery (SLNB, ALND), surgery of the breast (breast conserving surgery, mastectomy), radiation breast (no, yes), radiation axilla (no, yes) and chemotherapy (no, yes) was performed (Table 7).

ALND was a significant factor in the prediction in the majority of mean changes in the performed assessments of upper-limb function, ADL and QOL (Table 7). Radiation of the axilla was significant in four analyses: forward flexion, abduction, abduction/external rotation and arm volume (Table 7). Mastectomy was a predictor for the SDQ, QOL scales/items social functioning, appetite loss and body image and breast symptoms (Table 7). Chemotherapy was only a predictive variable for the decrease in sexual functioning (Table 7).

The increase in perceived disability in ADL (SDQ and GARS), the decrease in several functional scales and the increase of some symptom scales/items of QOL (QLQ-C30/QLQ-BR23) at two years after initial treatment were significantly correlated with increase in pain, decreased shoulder ROM, increased arm volume and in minor extent loss of strength in the same period (Table 8).

Table 3. Upper limb morbidity and disability two years after breast cancer treatment (n=181)

	Before surgery (mean ± SD)	2 years after surgery (mean ± SD)	Change (mean ± SD)	P value
Pain (VAS: 0 – 10)	0.4 ± 1.1	0.7 ± 1.4	0.3 ± 1.7	.01
Numbness (n)*	0 (0%)	114 (63%)	114	<0.001
Forward flexion (°)	172.4 ± 11.9	168.0 ± 13.5	-4.4 ± 12.6	<0.001
Abduction (°)	168.0 ± 22.6	151.8 ± 34.5	-16.2 ± 31.0	<0.001
Abduction / external rotation (°)	87.1 ± 6.6	81.1 ± 12.9	-6.0 ± 12.3	<0.001
External rotation (°)	67.7 ± 13.0	61.8 ± 12.7	-5.9 ± 13.6	<0.001
Strength shoulder abductors (Nm)	151.0 ± 36.8	141.0 ± 36.3	-10.0 ± 29.9	<0.001
Strength elbow flexors (Nm)	180.0 ± 40.7	185.8 ± 38.7	5.8 ± 40.5	.057
Grip strength (Nm)	297.8 ± 64.0	264.2 ± 69.1	-33.6 ± 51.7	<0.001
Volume arm (ml)	2162 ± 414	2286 ± 462	124 ± 241	<0.001
SDQ (0-100)	8.2 ± 19.7	18.7 ± 26.6	10.5 ± 29.9	<0.001
GARS (18-72)	19.6 ± 3.7	21.4 ± 6.2	1.8 ± 5.7	<0.001

Abbreviations: * No standard deviations were given because it concerns a dichotomous variable; (°): grades; Nm: Newton meter; ml: milliliter; SDQ: The Shoulder Disability Questionnaire[32]; GARS: The Groningen Activity Restriction Scale[33,34]; SD: standard deviation

Table 4. QOL (EORTC QLQ-C30 and QLQ-BR23 3 years after breast cancer treatment (n=181)

	Before surgery (mean ± SD)	2 years after surgery (mean ± SD)	Change (mean ± SD)	P value
Functional scales				
Physical functioning	91.3 ± 11.1	86.1 ± 15.8	-5.2 ± 13.3	<.001
Role functioning	92.4 ± 16.2	87.0 ± 21.7	-5.4 ± 23.8	.003
Emotional functioning	71.2 ± 19.9	87.0 ± 19.2	15.8 ± 20.7	<.001
Cognitive functioning	87.4 ± 15.5	86.3 ± 31.5	-1.1 ± 30.5	.624
Social functioning	92.3 ± 14.9	92.3 ± 16.7	0 ± 18.8	1.000
General Health Score QOL	80.4 ± 18.0	79.2 ± 19.2	-1.2 ± 19.8	.411
Symptom scales / items				
Fatigue scale	16.4 ± 20.2	20.6 ± 20.4	4.2 ± 17.5	.002
Nausea and vomiting scale	3.0 ± 11.1	4.7 ± 13.8	1.7 ± 16.1	.166
Pain scale	8.8 ± 17.5	14.9 ± 20.8	6.1 ± 21.4	<.001
Dyspnoea	5.8 ± 15.4	9.5 ± 21.3	3.7 ± 18.4	.007
Insomnia (sleeplessness)	23.7 ± 27.3	19.6 ± 26.7	-4.1 ± 29.4	.063
Appetite loss	7.5 ± 16.4	5.4 ± 15.9	-2.1 ± 20.1	.173
Constipation	2.6 ± 11.9	5.0 ± 13.9	2.4 ± 15.4	.037
Diarrhea	4.1 ± 12.1	2.6 ± 9.6	-1.5 ± 12.6	.117
Financial difficulties	1.7 ± 7.3	5.9 ± 21.2	4.2 ± 20.5	.006
QLQ-B R23 (Breast cancer module)				
Side effects	8.0 ± 8.4	12.8 ± 13.4	4.8 ± 13.2	<.001
Hair loss (only three patients)	22.2 ± 38.5	44.4 ± 38.5	22.2 ± 38.5	.423
Body image	94.7 ± 10.6	91.5 ± 17.7	-3.2 ± 17.1	.014
Future perspective	59.7 ± 25.1	72.4 ± 27.7	12.7 ± 28.2	<.001
Sexual functioning (n=137)	22.6 ± 20.1	23.8 ± 19.1	1.2 ± 19.3	.496
Sexual satisfaction (n=57)	56.8 ± 22.1	51.9 ± 23.9	-4.9 ± 27.0	.185
Arm symptoms	4.9 ± 10.2	13.7 ± 18.1	8.8 ± 19.4	<.001
Breast symptoms	10.9 ± 14.2	12.2 ±15.5	1.3 ± 18.1	.334

Abbreviations: EORTC: European Organization on Research and Treatment of Cancer, QLQ: quality of life questionnaire, SD: standard deviation

Table 5. Change of upper limb function and disability in the SLNB group and the ALND group between before surgery and two years after surgery

	SLNB (n=57) (t1-t0)	**ALND** (n=124) (t1-t0)	**Differences in mean change ALND-SLNB**	
Variable	Mean change ± SD	Mean change ± SD	Mean difference	**P value**
Pain (VAS: 0 – 10)	0.1 ± 1.4	0.4 ± 1.9*	0.3	.270
Numbness (n)[a]	10 (18%)	104 (84%)*	94	<0.001
Forward flexion (°)	-2.0 ± 9.5	-5.4 ± 13.6*	3.4	.094
Abduction (°)	-5.5 ± 21.0	-21.0 ± 33.5*	15.5	<0.001
Abduction / external rotation (°)	-3.5 ± 8.0*	-7.2 ± 13.7*	3.7	.025
External rotation (°)	-3.2 ± 12.9	-7.1 ± 13.8*	3.9	.076
Strength shoulder-abductors (Nm)	-7.1 ± 24.9*	-11.2 ± 32.0*	4.1	.400
Strength elbow-flexors (Nm)	14.2 ± 35.9*	2.0 ± 44.3	12.2	.063
Grip strength (Nm)	-17.2 ± 48.2*	-41.3 ± 51.7*	24.1	.004
Volume arm (ml)	-2 ± 142.5	182 ± 255.6*	184	<.0001
SDQ (0-100)	4.8 ± 24.1	13.2 ± 32.0*	8.4	.053
GARS (18-72)	0.2 ± 3.5	2.5 ± 6.3*	2.3	.002

Abbreviations: Results of t test for independent samples; [a] No standard deviations were given because it concerns a dichotomous variable; Nm: Newton meter; cm: centimeter; (°): degree; * significant changes between before and after surgery (P< .05); SDQ: The Shoulder Disability Questionnaire[32]; GARS: The Groningen Activity Restriction Scale[33,34]

Table 6. Change of QOL (EORTC QLQ C30 and QLQ-BR23) in the SLNB group and the ALND group between before surgery and two years after surgery

	SLNB (n=57) (t1-t0)	ALND (n=124) (t1-t0)	Differences in mean change ALND-SLNB	
Variable	Mean change ± SD	Mean change ± SD	Mean difference	P value
Functional scales				
Physical functioning	-.9 ± 10.6	-7.3 ± 13.9*	6.4	.001
Role functioning	-.3 ± 21.7	-7.8 ± 24.4*	7.5	.041
Emotional functioning	16.8 ± 22.5*	15.3 ± 19.8*	1.5	.649
Cognitive functioning	4.1 ± 14.5*	-3.5 ± 35.3	7.6	.118
Social functioning	.0 ± 12.3	.0 ± 21.2	.0	1.000
General Health Score QOL	1.1 ± 18.3	-2.3 ± 20.4	3.4	.302
Symptom scales / items				
Fatigue	1.4 ± 18.4	5.6 ± 16.9*	4.2	.133
Nausea	.9 ± 6.6	2.1 ± 19.1	1.2	.541
Pain	.6 ± 18.4	8.7 ± 22.4*	8.1	.012
Dyspnoea	3.0 ± 18.3	4.1 ± 18.5*	1.1	.706
Insomnia (sleeplessness)	-11.3 ± 27.9*	-.8 ± 29.6	10.5	.027
Appetite loss	-1.2 ± 16.6	-2.5 ± 21.6	1.3	.686
Constipation	.0 ± 17.8	3.5 ± 14.1*	3.5	.151
Diarrhea	-4.7 ± 17.2*	.0 ± 9.6	4.7	.059
Financial difficulties	2.9 ± 23.8	4.9 ± 18.9*	2.0	.554
QLQ-BR23 (Breast cancer module)				
Side effects	2.6 ± 11.6	5.8 ± 13.7*	3.2	.141
Body image	-4.0 ± 17.6	-2.9 ± 16.9	1.1	.692
Future perspective	13.9 ± 26.2*	12.1 ±29.2*	1.8	.693
Sexual functioning (n=129)	.9 ± 17.7	1.3 ± 20.1	.4	.914
Sexual satisfaction (n=57)	9.8 ± 19.6	2.7 ± 29.8	7.1	.375
Arm symptoms	3.0 ± 11.5	11.5 ± 21.7*	8.5	.001
Breast symptoms	.0 ± 17.5	1.9 ± 18.4	1.9	.517

Results of t test for independent samples

Abbreviations: * significant changes between before and after surgery (P< .05), SD: standard deviation

Table 7. Prediction of mean change in upper-limb function, ADL and QOL between before surgery and two years after surgery by means of linear regression analysis for independent variables: patient age, axillary surgery (SLNB=0, ALND=1), surgery of the breast (breast conserving surgery=0, mastectomy=1), radiation breast (no=0, yes=1), radiation axilla (no=0, yes=1) and chemotherapy

Dependent	Independent	ß (95% CI)	r^2 change
Assessments:			
Pain (VAS)			
	Patient age	.02 (0.0 to 0.05)	.03
	Constant	1.1 (-.2 to 2.4)	
Forward flexion (°)			
	Radiation axilla	7.9 (1.1 to 14.7)	.03
	Constant	3.5 (1.6 to 5.3)	
Abduction (°)			
	Radiation axilla	21.9 (4.8 to 39.0)	.05
	ALND	12.6 (3.0 to 22.2)	.03
	Constant	5.5 (-2.3 to 13.3)	
Abduction / external rotation (°)			
	Radiation axilla	10.8 (4.2 to17.5)	.06
	Patient age	.2 (0.0 to 0.3)	.02
	Constant	-3.7 (-12.5 to 5.1)	
Grip strength (Nm)			
	ALND	23.7 (7.6 to 39.9)	.05
	Constant	1.7 (0.4 to 3.1)	
Volume arm (ml)			
	ALND	166 (94 to 238)	.13
	Radiation axilla	165 (26 to 304)	.03
	Constant	-2.1 (-61 to 56)	
Shoulder disability questionnaire			
	ALND	9.8 (0.5 to 19.0)	.02
	Mastectomy	-13.0 (-21.8 to -4.2)	.03
	Constant	8.6 (0.7 to 16.6)	
Groningen Activity Restriction Scale			
	ALND	2.1 (0.4 to 3.9)	.03
	Constant	0.2 (-1.2 to 1.6)	
Physical functioning			
	ALND	6.0 (2.0 to 10.1)	.05
	Constant	0.9 (-2.4 to 4.2)	
Social functioning			
	Mastectomy	-6.0 (-11.6 to -0.4)	.03
	Constant	2.2 (-1.3 to 5.8)	
Pain scale (QLQ C30)			
	ALND	8.1 (1.3 to 14.9)	.03
	Constant	0.6 (-5.0 to 6.1)	
Insomnia (sleeplessness)			
	ALND	10.5 (1.1 to 19.8)	.03
	Constant	-11.3 (-19.0 to 3.6)	
Appetite loss			
	Mastectomy	6.3 (0.3 to 12.4)	.02
	Constant	-0.6 (-4.4 to 3.2)	
Diarrhea			
	ALND	4.7 (0.7 to 8.7)	.03
	Constant	-4.7 (-8.0 to 1.4)	
Body image			
	Mastectomy	9.2 (4.0 to 14.3)	.07
	Constant	-0.6 (-3.8 to 2.7)	
Sexual functioning			
	Chemotherapy	7.9 (1.1 to 14.8)	.04
	Constant	-4.3 (-8.6 to 0.0)	
Arm symptoms			
	ALND	7.6 (1.8 to 13.4)	.04
	Constant	3.0 (-1.8 to 7.7)	
Breast symptoms			
	Mastectomy	-8.3 (-13.7 to 2.9)	.05
	Constant	4.5 (1.1 to 7.9)	

Abbreviations: Only significant predictors are represented; CI: confidence interval

Table 8: Correlations between long-term upper limb morbidity and perceived disability in ADL (SDQ and GARS) and poorer QOL (QlQ-C30 and QLQ-BR23) two years after treatment of breast cancer patients (n=181)

	VAS t0-t1	Abd t0-t1	Forw fl t0-t1	Abdext t0-t1	Ext rot t0-t1	Grip str t0-t1	Str abd t0-t1	Str E fl t0-t1	Arm vol t0-t1
SDQ	.476**	-.470**	-.396**	-.372**	-.131	-.020	-.185*	-.258**	.241**
GARS	.362**	-.336**	-.435**	-.437**	-.106	.014	-.036	-.061	.127
Functional scales EORTC QlQ-C30									
PF	-.371**	.331**	.331**	.319**	.176*	.108	.143	.169*	-.099
RF	-.278**	.378**	.506**	.484**	.158*	-.005	-.150*	.197**	-.204**
CF	-.091	.254**	.282**	.240**	.094	-.084	.055	.112	-.304**
SF	-.123	.201**	.223**	.177*	.124	.058	.168*	.089	.085
GHS	-.201**	.150*	.194*	.213**	.249**	-.008	.037	.150*	-.092
Symptom scales / items									
FA	-.325**	.060	.086	.070	.139	-.051	.042	.091	-.166 *
PA	-.600**	.321**	.363**	.350**	.101	.004	.200**	.256**	-.361**
QLQ-BR23 (Breast cancer module)									
SE	-.219**	.042	.228**	.230**	.077	.021	.148	.065	-.036
AS	-.406**	.546**	.477**	.542**	.229**	.020	.170*	.200**	-.401**
BS	-.334**	.144	.201*	.199**	.046	-.070	.123	.147	-.186 *

Abbreviations: Only scales of ADL and QOL assessment with significant correlations are presented. ** significant p≤ .001; * significant p≤.005; VAS: visual analogue scale; Abd: abduction; Forw fl: forward flexion; Abdext: abduction/external rotation; Ext rot: external rotation; Grip str: grip strength; Str abd: strength abductors; Str E fl: strength elbow flexors; Arm vol: arm volume; SDQ: shoulder disability questionnaire; GARS: groningen activity restriction scale; PF: physical functioning; RF: role functioning; CF: cognitive functioning; SF: social functioning; GHS: global health status; FA: fatigue; PA: pain; SE: side effects; AS: arm symptoms; BS: breast symptoms.

Discussion

This study showed significant long-term upper limb morbidity, associated ADL disability and also decreased QOL in breast cancer patients undergoing SLNB and/or ALND two years after treatment. Patients undergoing SLNB had significantly less long-term upper limb morbidity, ADL disabilities and declination of some items of QOL two years after treatment compared to patients undergoing ALND. In the assessment of changes in upper limb function, ADL and QOL, ALND is the most frequent found predictor of deterioration. Long-term upper limb morbidity is significantly correlated with disabilities in ADL and worsening of QOL.

This outcome confirms the assumption that SLNB is a less extensive surgical procedure, associated with less upper limb morbidity, less disabilities in ADL and a

better QOL compared to ALND. This is the first prospective study comparing SLNB and ALND with pre- and long-term post surgical assessments of upper limb function, ADL and QOL. Although several studies previously reported less morbidity in patients after SLNB compared to ALND, only four studies used a pre-operative assessment.[12,15,18,21] Also there was considerable variability in study design, follow up period and use of assessment instruments. ADL was assessed in only three studies.[13,16,21] Assessment of QOL in comparison between SLNB and ALND was performed in two studies.[19,21]

In a recent systematic review and two previous studies we emphasized the importance of the baseline assessment and the use of reliable and validated assessment instruments.[6,37,38] The current study used a pre-operative assessment. Additionally several reliable and validated measurement instruments were used to assess upper limb morbidity, perceived disability in ADL and QOL.[25-36]

This study showed that patients undergoing SLNB had significantly less long-term (2 years after surgery) upper limb morbidity compared to ALND. Significant differences between the groups concerned numbness, shoulder ROM in abduction, abduction/external rotation, grip strength and arm volume. Decrease in upper limb function in the SLNB group was only significant for ROM in abduction/external rotation, strength shoulder-abductors and grip strength. This outcome confirms results of previous studies suggesting that SLNB is associated with less treatment related upper-limb morbidity although these are no long-term comparative studies.[12-19,21,37,38]

The perceived disabilities in ADL assessed in this study with the SDQ and GARS are significant but relatively mild. The difference in mean change of ADL between pre surgery and two years after surgery comparing SLNB and ALND is significant using the GARS but not for the SDQ. The GARS assesses general ADL and the SDQ assesses more shoulder related ADL. This outcome is in contrast to the expectations and difficult to explain. Two other studies assessed interference with ADL although up till one year after treatment.[16,21] Both studies found no difference in interference with daily life between the groups, probably due to a relative small patient sample size (n=56) or the different assessment instruments (KPS [Karnofsky performance status scale] and a self constructed questionnaire versus SDQ/GARS) which might be less sensitive for detecting small changes.[16,21]

Concerning QOL for the entire study group a significant decrease was found over the two years for physical and role functioning and body image whereas emotional functioning and future perspective showed significant increase over this period (Table 4). The improvement of emotional functioning and future perspective can be explained by the fact that the first assessment took place one day before surgery. Obviously at this time patients were nervous and stressed and also uncertain about their future perspective.[21] Two years later these aspects were highly improved.

Some scores on symptom scales increased significantly such as fatigue, pain, dyspnoe, constipation, side effects of systemic therapies and arm problems (Table 4).

This outcome corresponds with results found in earlier studies done on breast cancer treatment and QOL.[6-8,21]

Comparing SLNB and ALNB significantly differences in mean change over the two years were found for physical and role functioning and also for symptom items such as pain, insomnia (sleeplessness) and arm symptoms in favor for the SLNB group (Table 6). All significant changes over the two years after treatment in the SLNB group (emotional functioning, cognitive functioning, sleeplessness, diarrhea and future perspective) are for the better (Table 6). All significant changes over the two years after treatment in the ALND group (physical functioning, role functioning, fatigue, pain, dyspnoea, constipation, financial difficulties, side effects and arm symptoms) are for the worse except emotional functioning and future perspective (Table 6).

Comparing our results with those of Peintinger et al 2003 there is some agreement about the improvement of emotional functioning and future perspective during post surgery follow-up period although they found no significant differences.[21] Also the decrease in physical and role function and a worsening of body image and pain was described but contrary to our results they found no statistically significant differences in any dimension of QOL during the follow up period or between SLNB and ALND, 9-12 months after surgery.[21] Probably this was caused by their relative small patient sample size (n=56).

Nevertheless the interpretation of the scores on the EORTC QLQ-C30 and QLQ-BR23 in relation to clinical relevance needs some discussion. Comparing our data of the EORTC QLQ-C30 with normative data from the Swedish and German female population with the same mean age, there are small but significant differences between the study group and these healthy populations as well before surgery and two years after surgery for some of the functional and the symptom scales.[39,40] Two years after treatment the study group has a higher score for emotional functioning and global health scale but a lower pain and dyspnoe score. This implies that QOL of breast cancer patients will be defined by there frame of reference and is approximately comparable with QOL of a healthy population of the same mean age.

But how to interpretate the significant changes of QOL scores within the groups and the difference of change between the SLNB and the ALND group? King did a review on the interpretation of scores from the EORTC QLQ-C30 and tried to explicit clinically relevant difference before and after treatment and between treatment groups.[41] He stated that the smallest clinically important difference may vary with clinical context. All the statistically significant differences found in our study within and between the groups could be interpretated as relatively small clinically important differences except the improvement of emotional functioning which could be interpretated as a very large clinically important difference.[41]

Multivariate linear regression analysis to predict mean change in upper-limb function, ADL and QOL between before and two years after surgery showed that

radiation on the axilla is a significant factor in the prediction of impaired ROM (Table 7). The effect of radiation on the axilla was most outspoken for shoulder abduction, combined abduction/external rotation, forward flexion and increase of arm volume. This is in conformation with results of some other studies and may be explained by radiation induced subcutaneous fibrosis affecting the ROM and lymph drainage.[6,8,42,43] The fact that patients who received radiation on the axilla naturally belonged to the ALND group may influence the comparison between SLNB and ALND concerning treatment related morbidity. ALND as predictor of upper limb morbidity was observed for abduction, grip strength, arm volume, ADL and some scales of the QLQ-C30 and QLQ-BR23. This result confirms results of other studies in which the extent of axillary treatment was found to be related to late morbidity.[6,19,20,42]

Although the comparison between mastectomy and breast conserving surgery was not subject to this study we found that mastectomy predicts a part of the decrease in body image but breast conserving surgery is more associated with breast symptoms (Table 7). A lower body image in mastectomy patients was earlier described.[44]

A relative strong correlation exists between upper limb morbidity (pain, shoulder ROM and edema) and reduction in ADL, physical and role functioning and increase of the pain and arm symptom scale of the EORTC QLQ-C30 and QLQ-BR23. Change in strength of the upper limb is less correlated with disabilities in ADL and reduction in QOL (Table 8).

Conclusion

Significant treatment related upper limb morbidity, associated ADL disabilities and decreased QOL exist two years after SLNB or ALND. Treatment related upper limb morbidity, perceived disabilities in ADL and worsening of QOL two years after surgery is significantly lower after SLNB compared to ALND. In the assessment of changes in upper limb function, ADL and QOL, ALND is the most frequent found predictor of deterioration. Additional radiation on the axilla predicts a further decrease in shoulder ROM and arm edema. Long-term upper limb morbidity is significantly correlated with disabilities in ADL and worsening of QOL.

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CHAPTER 9

General discussion and conclusions

Introduction

The primary aim of the thesis was to study upper limb morbidity, perceived disabilities in ADL and QOL till two years after onset of breast cancer treatment comparing patients with ALND and patients without ALND, the so called SLNB patients.

Answers on the research questions formulated in the introduction are incorporated in this general discussion and the most important findings of the studies performed will be united and discussed on their clinical relevance and implications. Also weaknesses of the studies and alternative research strategies are elucidated and discussed. Furthermore, recommendations for future research are provided.

Discussion

Systematic review and retrospective study

In the first part of the thesis (Chapter 2) we performed a systematic review on late morbidity after treatment of breast cancer in relation to ADL and QOL. In addition a retrospective study was performed on the same subject (Chapter 3). In the review we used a self constructed list of criteria for the assessment of the methodological quality of the selected studies. The reason for this choice was to emphasize not only the general methodological criteria but especially the reliability and validity of measurement instruments used to assess late morbidity, ADL and QOL in breast cancer patients. To our disappointment, in the last 20 years (till 2000) there were just a few studies investigating the relationship between late morbidity of the upper limb and perceived disabilities in ADL and/or QOL.

The overall methodological quality of these studies was limited. Little attention was paid to reliability and validity of the assessment tools and in only two studies a pre-treatment baseline assessment was performed.[1,2] Six studies fulfilled one third of the estimated methodological criteria and were reviewed in detail.[1-6] Remarkable was the wide variability in assessment instruments for as well upper limb morbidity as ADL and QOL. The lack of uniformity and reliability/validity of these instruments weakened the results of the studies and made comparison of the study results difficult. Although these six articles described significant relationship between late morbidity after treatment of early breast cancer and restrictions of daily activities and poorer QOL, the strength of this relationship was low or not given and clinical relevance was poorly investigated.

In order to give better answers on the research questions, a retrospective study was performed to assess long-term upper limb morbidity, perceived disabilities in ADL and QOL after treatment of breast cancer and to analyze the relationship between

treatment modalities, upper limb morbidity, perceived disabilities in ADL and QOL (Chapter 3). In this study reliable and validated assessment instruments were used and clearly described. Also impairments were clearly defined; pain as a score on the VAS > 0.0, a difference in range of motion between the affected side and non-affected side of ≥ 20 , difference in grip strength between affected and non-affected side of ≥ 10% and a difference in arm volume between affected and non-affected side of ≥ 10% was considered as lymphedema. Within these definitions the study provided prevalence of impairments: pain (60%), in shoulder forward flexion (9%), in shoulder abduction (16%), in shoulder external rotation (11%), in grip strength (40%) and lymphedema of the arm (15%). Although prevalence of these impairments lie within the range of prevalence of studies referred in our systematic review, adequate comparison remains difficult because the different assessment methods and definitions of impairments used.

When the impairments are used to predict perceived disabilities in ADL, pain explained 61% and decreased shoulder range of motion explained 12% of the variance in disability score measured with the SDQ. Contrary to our expectations and outcomes of a previous study, no relation was found between lymphedema and perceived disabilities in ADL.[2] Due to the relative mild character of the impairments, they apparently do not result in a high state of disability. Health related QOL (RAND-36) was in lesser extend predicted by impairments in which pain was the most important factor followed by grip strength and shoulder range of motion. This lower association between impairments and QOL compared to impairments and ADL might be explained from the fact that impairments will interfere more with ADL than with health related QOL.

Despite the fact that this study provided prevalence of impairments and showed relationship between impairments and disabilities in ADL and health related QOL, we are aware of the weaknesses of the study. The absence of a pre-treatment assessment due to the retrospective design of the study and the relative small number of participating patients (n=55) make that the results should be interpreted with caution.

Prospective study

The second part (Chapters 4 and 5) forms together with Chapter 8 the main subject of the thesis. It concerns a longitudinal prospective study in which short-term, middle-term and long-term upper limb morbidity, perceived disabilities in ADL and QOL were assessed before and up till two years after SLNB or ALND for breast cancer.

SLNB was introduced, just prior to the onset of our study, for staging of the axilla to reduce the number of unnecessary ALND's and proved to be an accurate and safe procedure to predict metastatic disease in clinically negative axillary lymph nodes.[7-9] SLNB was expected to have less treatment related morbidity in comparison to ALND.[10-18] To our knowledge, till now no prospective study is performed comparing SLNB and ALND with pre surgical assessment and short-, middle- and long-term post

surgical assessments of upper limb function, ADL and QOL. As mentioned in the Chapters 4, 5 and 8, reliable and valid assessment instruments were used for assessment of upper limb morbidity, ADL and QOL. For assessment of QOL we chose a cancer specific health related QOL questionnaire (EORTC QLQ-C30 questionnaire supplemented with the breast module EORTC QLQ-BR23) which has been devised specifically for breast cancer patients.[19] This questionnaire was designed for use among breast cancer patients in a wide range of disease stages, undergoing different treatments to detect clinically meaningful changes in QOL over time.[20]

Because a pre-treatment assessment was performed, it was possible to focus on the changes which took place in upper limb function, ADL and QOL. At all post surgical assessment moments (6 weeks, 1 year and 2 years) treatment-related upper limb morbidity and associated disabilities in ADL were observed for the entire study group.

Interesting from a clinical point of view are the changes in upper limb function and ADL in time after treatment of breast cancer. Pain, range of motion of the shoulder, strength of shoulder abductors and elbow flexors and ADL (SDQ and GARS) showed largest changes at 6 weeks after surgical treatment. At 1 year after treatment there is some reduction of these changes after which they remain relatively stable until at least 2 years after treatment. In this perspective, upper limb morbidity and associated disabilities in ADL are at worse in the early stage (first months) after surgical treatment of breast cancer after which some but incomplete recovery will take place. This phenomenon was also described in two earlier studies but these studies had a much shorter follow up period.[21,22] Later on in this discussion, involvement of physiotherapy in the pre- and postoperative period will be discussed.

The reduction in grip strength showed however an increase over the 2 years without signs of recovery. No other study described this progression in loss of grip strength although a long-term reduction of grip strength was found.[1,4] Maybe this progressive loss of grip strength is due to a reduction of performed functional tasks in which continuous grip strength is required of the affected side, according to advices of lymphedema prevention programs.

As expected, arm volume increased after the first assessment and significantly increased at 1 and 2 years follow up. Two forms of lymphedema have been described in literature. Early lymphedema occurs within months after surgery and results from acute lymphatic overload and is associated with wound complications.[23] Although in this study, 26 of the 198 patients (13%) were complicated with inflammation of the wound that necessitated antibiotic treatment, no early lymphedema occurred. Late lymphedema can start any time after 6 months from surgery and is often progressive.[23,24] It is caused by lymphatic obstruction, whether by surgical interruption or fibrosis.[23] The role of axillary surgery and radiation therapy in the development of lymphedema will be discussed later.

Changes in QOL assessed with the EORTC QLQ-C30 / QLQ-BR23 were described only at 2 years after surgical treatment. Concerning QOL for the whole

study group a significant decrease was found over the two years for physical and role functioning and body image whereas emotional functioning and future perspective showed significant increase over this period. The improvement of emotional functioning and future perspective can be explained by the fact that the first assessment took place one day before surgery. Obviously at this time patients were nervous and stressed and also uncertain about their future perspective.[22] Two years later these aspects were considerably improved.

ALND versus SLNB

At all post surgery assessments (6 weeks, 1 year, 2 years), patients undergoing SLNB had significantly less upper-limb morbidity and ADL disabilities compared to patients undergoing ALND. After 2 years patients undergoing SLNB had also significantly less declination of some items of QOL (physical- and role functioning, pain and sleeplessness and arm symptoms) compared to patients undergoing ALND. This outcome confirms the assumption that SLNB is a less extensive surgical procedure, associated with less upper limb morbidity, less disabilities in ADL and a better QOL compared to ALND.

In longitudinal perspective, changes in upper limb function and ADL of both groups (ALND and SLNB) showed comparable trends as mentioned for the total study group, only the changes in the ALND patients are larger compared with the SLNB patients. Up till 1 year after surgery there are significant differences in change between the ALND group and SLNB group for numbness, shoulder forward flexion, abduction, abduction/external rotation, strength of shoulder abductors, strength of elbow flexors, grip strength and ADL. No significant differences were found for pain (VAS) and shoulder external rotation. From 1 year also a significant difference in change of arm volume was found. At 2 years after ALND or SLNB there are still significant differences in change of numbness, shoulder abduction, abduction/external rotation, grip strength, arm volume and ADL in favor of the SLNB group. The mean increase in arm volume over the 2 years in the ALND group was in fact 182 ml. Lymphedema can be defined as an increase of arm volume $\geq$ 200 ml.[23]

The ALND patients showed at 2 years after surgery still significant reduction of all aspects of upper limb function and ADL except strength of elbow flexors and SLNB patients only for abduction/external rotation, strength of shoulder abductors and grip strength.

Although mean upper limb morbidity and perceived disabilities in ADL after ALND were relatively mild, the chronic character is alarming. In this context it is important to discuss our statistical methodology. We have chosen for t-test for independent samples for between group comparison and t-test for dependent samples for within group comparison. This is the preferable method for comparison of means of different groups; however it gives no information of the individual patients within the groups. We might have used the methodology of chapter 3 in which prevalence of

defined impairments were calculated. Variability in upper limb morbidity and disability in ADL within the SLNB group or ALND group is expectable and thus the presence of patients with chronic moderate to substantial upper limb morbidity and perceived disabilities in ADL after ALND.

Concerning QOL, significantly differences in mean change over the two years comparing SLNB with ALND were found for physical and role functioning and also for symptom items such as pain, insomnia (sleeplessness) and arm symptoms in favor of the SLNB group. QOL in the SLNB group was just improving in the 2 years after treatment whereas in de ALND group only emotional functioning and future perspective improved but physical functioning, role functioning, fatigue, pain, dyspnoea, constipation, financial difficulties, side effects and arm symptoms deteriorated. This outcome is of great clinical importance, because it may help health care planners to determine at risk patient groups and to develop specialized patient services.

Nevertheless, the interpretation of the scores on the EORTC QLQ-C30 and QLQ-BR23 in relation to clinical relevance needs some discussion. QOL of breast cancer patients and the changes in QOL are influenced by their frame of reference and therefore a cross-sectional design as used in Chapter 3 has some disadvantages. Also comparison of the patients QOL scores with those of normative data from a general population, as we did in Chapters 3 and 8, is for the same reason not without problems. However even a longitudinal design does not necessarily guarantee an unbiased assessment of changes in QOL in the course of time.[20] Possible confounding events could not be excluded, but those events occurred in the ALND as well as in the SLNB patient group.

The statistical significant changes of QOL scores within the groups and the difference of change between the SLNB and the ALND group needs some clinically interpretation. King (1996) did a review on the interpretation of scores from the EORTC QLQ-C30 (not the EORTC QLQ-BR23) and tried to explicit clinically relevant change before and after treatment and difference between treatment groups.[25] He stated that the smallest clinically important change may vary with the clinical context. All the statistically significant mean changes found in our study within and the differences between the groups can be interpretated as relatively small clinically important changes except the improvement of emotional functioning which could be interpretated as a very large clinically important change.[41] When this interpretation is extrapolated to the QLQ-BR23, also the increase of arm symptoms and improvement of future perspective could be interpretated as clinically important.

Multivariate linear regression analysis to predict mean change in upper-limb function, ADL and QOL by treatment variables was performed at 6 weeks, 1 year and 2 years. Analysis at 1 and 2 years showed that radiation therapy on the axilla is besides ALND an important factor in the prediction of impaired shoulder ROM and arm edema. Radiation therapy on the breast had no influence on shoulder ROM. At 6

weeks after surgery, radiation therapy on the breast was not yet performed or finished, but at that time mastectomy was also a variable predicting short-term morbidity.

The effect of axillary radiation therapy on shoulder ROM and arm volume has been described earlier.[5,26] Radiation therapy induced subcutaneous fibrosis was held responsible for the reduced ROM and the reduced lymph drainage. The fact that patients who received radiation therapy on the axilla naturally belonged to the ALND group influences the differences between SLNB and ALND concerning treatment related morbidity. Both treatment variables, ALND and radiation therapy on the axilla are clinically important factors associated with middle-term and long-term upper limb morbidity. ALND is also a significant predictor of perceived disabilities in ADL and worsening of some scales (physical functioning, pain, sleeplessness, diarrhea and arm symptoms) of the QLQ-C30 and QLQ-BR23. These results confirm results of other studies in which the extent of axillary treatment was found to be related to late morbidity.[5,17,18]

The multivariate regression analyze showed also that after 2 year a relationship exists between mastectomy and lower body image. This relation between mastectomy and lower body image is also found in earlier studies.[27] Patients who had breast conserving treatment seems to have less negative attitude regarding body image than patients treated by mastectomy.

Concerning the mastectomy patients in this cohort we recorded also the incidence of phantom breast sensations (PB sensations) and phantom breast pain (PB pain) during the 2 year follow up and we assessed how much patients were bothered by PB sensations and PB pain (Chapter 6). Over time the percentage of patients with PB sensations remained relatively stable (around 20%) but for PB pain the percentage reduced from 7% to 1%. Contrary to patients with a lower or upper limb amputation, mastectomy patients were hardly bothered by PB sensations or PB pain so these phenomena are of little clinical relevance in the 2 years following mastectomy.

Relationship upper limb morbidity, disabilities in ADL and QOL

A relative strong correlation exists between upper limb morbidity (pain, shoulder ROM and edema) and reduction in ADL, physical and role functioning and increase of the pain and arm symptom scale of the EORTC QLQ-C30 and QLQ-BR23. We stated earlier that mean impairments (upper limb morbidity) and disabilities in ADL were relatively mild. Also overall mean changes in QOL were of relatively small clinical relevance except the improvement of emotional functioning and future perspective and the increase of arm symptoms. However, within the variation of patients treated for early breast cancer, there will be patients with considerable upper limb morbidity with clear relations to perceived disabilities in ADL and worsening of QOL at least up till 2 years after treatment.

Clinical implications

In terms of clinical relevance, results of this study provided criteria by which patients at risk for upper limb morbidity could be determined by their treatment variables (ALND and axillary radiation therapy) and should be offered appropriate therapy and support.

Although there is still no consistent agreement on the value of pre- and postoperative physiotherapy programs, there is some evidence that an early provided exercise program realizes earlier recovery of shoulder ROM compared to a delayed provided exercise program.[28] Appropriate physiotherapy should be provided during hospital stay for these 'at risk' patients mainly to instruct them for arm exercises and ADL.[21,28] Patients with early upper limb morbidity should continue physiotherapy in the early postoperative period. Especially patients, who had additional axillary radiation therapy, should also be examined in the later follow-up period to determine possible upper limb morbidity, eventually followed by physiotherapy or treatment of lymphedema.

At the same time, psycho-oncological care should be provided not only during hospital stay and in the early postoperative phase but also if needed after completion of therapy and in the long-term follow up.[20]

Patients, who had a SLNB and breast conserving therapy, are not at risk for short-term, middle-term and long-term upper limb morbidity, associated disabilities in ADL and reduction of QOL, and probably will not need physiotherapy. A printed illustrated instruction form with arm exercises should be appropriate for the majority of these patients.

Patients with a SLNB and mastectomy are relatively at risk for short-term upper limb morbidity but not for middle-term and long-term upper limb morbidity. During hospital stay and maybe a short period after that, supervised physiotherapeutic exercise sessions should be provided. However, these patients are at risk for lower body image so psycho-oncological support may be necessary.

Because the long-term effects on QOL, integration of psycho-oncological support into the somatic treatment to ensure comprehensive care for breast cancer patients, is indicated. This should be a task of the surgical-oncology team in cooperation with rehabilitation medicine.

Recommendations for future research

Because results of this study showed limited upper limb morbidity, perceived disabilities in ADL or worsening of QOL in patients after SLNB up till 2 years after treatment, no further comparative studies with this follow up period need to be done. However, future research can be focused on longer follow up with the same or comparable assessment instruments. Also important, seems to assess more discriminative prediction variables for upper limb morbidity and associated problems of ADL and QOL. Finally, future research should be done on the effectiveness of integrated somatic and psycho-oncological rehabilitation programs for breast cancer patients on impairments, disabilities and QOL in a long-term longitudinal research setting.

Conclusions

To return to the research questions formulated in the introduction of this thesis we conclude:

1. In literature a significant relationship between late morbidity after treatment of early breast cancer and restrictions of daily activities and worsening of QOL is described. The strength of this relationship is weak or not given and clinical relevance is poorly investigated.
2. Significant treatment related short-term, middle-term and long-term upper limb morbidity and perceived disabilities in ADL and long-term reduction of QOL exist in breast cancer patients.
3. Treatment related upper limb morbidity, perceived disabilities in ADL and worsening of QOL up till two years after surgery is significantly less after SLNB compared to ALND.
4. In the assessment of changes in upper limb function, ADL and QOL, ALND is the most frequent found predictor of deterioration. Additional radiation therapy on the axilla predicts a further decrease in shoulder ROM and arm edema.
5. Long-term upper limb morbidity is significantly correlated with disabilities in ADL and worsening of QOL. Clinical relevance of this correlation is clearly demonstrated.

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SUMMARY en SAMENVATTING

Summary

This thesis describes treatment related upper limb morbidity, perceived disabilities in activities of daily life and quality of life in breast cancer patients.

In **Chapter 1**, the introduction of the thesis, primary aim, outline and main research questions are formulated. Breast cancer treatment is from its early beginning associated with upper limb morbidity including pain and numbness, reduced range of motion of the shoulder, muscle weakness of the arm and hand and lymph edema. Primarily the surgical treatment of the axilla (axillary lymph node dissection [ALND]) gives rise to long-term problems with shoulder movement and lymph edema of the arm. Additional radiation therapy of the axilla may increase upper limb morbidity due to late normal tissue radiation injury. In the early nineties sentinel lymph node biopsy (SLNB) was introduced for staging of the axilla and nowadays SLNB is an excellent alternative for ALND in patients with clinically negative lymph nodes. Research that has been performed to evaluate SLNB related morbidity in comparison to ALND related morbidity, reported less morbidity for SLNB in comparison to ALND. A general methodological shortcoming in these studies is the absence of pre-treatment assessment and the absent of reliable and valid assessment instruments. Also the relationship between treatment modalities and treatment related upper limb morbidity and Activities of Daily Life (ADL) and Quality of Life (QOL) was scarcely subject of study in the past.

Thus it was necessary to perform a prospective long-term cohort study which assesses and analyses treatment related upper limb morbidity, ADL and QOL, with reliable and valid assessment instruments, comparing breast cancer patients with SLNB with breast cancer patients treated with ALND.

This thesis addresses the extent of treatment related upper limb morbidity, their relation to ADL and QOL, predictive treatment variables, phantom breast sensations and phantom breast pain after mastectomy and the validity and reliability of a method of indirect volume measurement.

The main research questions answered in this thesis are:

1. What is known in literature about upper limb morbidity in relation to ADL and QOL after breast cancer treatment?
2. What are the short-term, middle-term and long-term upper limb morbidity and perceived disabilities in ADL after breast cancer treatment?
3. What are the changes in QOL two years after onset of breast cancer treatment?
4. What are the differences between SLNB and ALND concerning upper limb morbidity, perceived disabilities in ADL and QOL?
5. Which treatment variables can predict upper limb morbidity, perceived disabilities in ADL and reduction of QOL?

6. What is the relationship between upper limb morbidity, perceived disabilities in ADL and QOL?

Chapter 2 describes a systematic review which was performed to evaluate the results of studies, analyzing late morbidity of breast cancer treatment in relationship with ADL and/or QOL. A literature search over the last 20 years (1980-2000) was performed in the databases MEDLINE, EMBASE, PSYCHLIT and CANCERLIT. Methodological quality of selected articles was assessed and additional, aspects of treatment related late morbidity and the relationship to ADL and/or QOL were analyzed.

Of the 1642 papers identified, only 15 fulfilled the primary selection criteria concerning stage of breast cancer, treatment modalities, interval between surgical treatment and assessment of late morbidity and relationship of this late morbidity with ADL and/or factors of QOL. The overall methodological quality of these papers was limited. Little attention was paid to reliability and validity of the assessment tools and surprisingly only two studies applied a pretreatment baseline measurement.
Six articles fulfilled one third of the estimated methodological criteria and could be selected for further analysis. There was a great variability in the applied assessment instruments for impairments as well as for ADL. In addition, no uniform criteria exist for reporting impairments in pain, range of motion, volume or muscle strength.

The reported prevalence of impairments were highly variable: pain (12-51%), impairments in range of motion (2-51%), edema (6-43%) and decreased muscle strength (17-33%). Significant relationships between late morbidity and restrictions of daily activities and poorer QOL were reported, however, the strength of this relationship was low and the clinical relevance was not reported.

The aim of the study presented in **Chapter 3** was to assess impairments, disabilities and health related QOL after treatment of breast cancer and to analyze the relationship between treatment modalities, impairments, disabilities and health related QOL.

In this retrospective study, 55 patients who underwent a modified radical mastectomy or a segmental mastectomy with axillary lymph node dissection were assessed averagely 2.7 years after treatment. Impairments were assessed by means of measuring active shoulder range of motion, grip strength, arm volume and pain. Disabilities were assessed by means of the Shoulder Disability Questionnaire (SDQ) and health related QOL was assessed by means of the RAND 36-item Health Survey (RAND-36). Pain (60%) and reduction of grip-strength (40%) were the most frequent impairments found. The prevalence of impaired range of motion was 16% and of edema the prevalence was 15%. Mean scores of the RAND-36 were significantly lower for physical functioning, vitality and health perception compared to that of a female norm group. Only radiotherapy and to a minor extent chemotherapy were significant related to impaired range of motion. When the impairments are used to

predict disabilities, pain explained 61% of the variance in disability score (SDQ) and range of motion (forward flexion and external rotation) explained 12% of the variance in disability score. In the prediction of health related QOL; pain, grip strength and arm volume were significantly related to health related QOL for six, three and two domains.

Weaknesses of the study were the rather low response and the absence of a pre-treatment baseline assessment. Implications for rehabilitation practitioners are enclosed in the relatively moderate impairments of which pain and reduced range of motion of the shoulder are related to mild disabilities and some domains of health related QOL.

The objective of the study described in **Chapter 4** was to analyze prospectively the short-term upper limb morbidity and perceived disabilities in ADL in patients after SLNB compared to patients after ALND.

The study comprised 204 patients with stage I/II breast carcinoma of which 198 patients completed pre- and postoperative assessments, 62 with SLNB and 136 with ALND. Contemporary surgical treatment included a modified radical mastectomy or breast-conserving treatment.

Upper-limb function and ADL were evaluated 1 day before surgery and 6 weeks after surgery. Pain was assessed with a visual analog scale. Active shoulder range of motion (ROM) was measured with a goniometer according to a standardized protocol. Muscle strength of the shoulder abductors and elbow flexors was measured using a hand-held dynamometer and grip strength were measured with a Yamar hand-held dynamometer. Upper and forearm circumference was measured with a Gulick measuring tape. ADL was assessed with the SDQ and the Groningen Activity Restriction Scale (GARS).

Considerable treatment related upper-limb morbidity was observed for the entire study group. Significant changes were found for pain, range of motion in forward flexion, abduction and abduction / external rotation, strength of shoulder abductors and elbow flexors and in perceived disabilities in ADL. Six weeks after surgery, numbness was observed in 14 patients in the SLNB group (23%) and in 119 patients in the ALND group (87%). Decrease in forward flexion, abduction, abduction / external rotation, grip strength, strength of shoulder abductors and elbow-flexors and increase of the GARS score were significantly larger in the ALND group compared to the SLNB group. ALND and to a minor extent mastectomy were significant factors in the prediction of shoulder related upper limb morbidity and perceived disabilities in ADL (GARS). Impairments that significantly correlated with perceived disabilities in ADL post surgery were pain, decreased shoulder ROM and to a minor extent loss of strength.

Chapter 5 attends to the same objective as described in chapter 4 but with a follow up of one year after surgery. Identical assessment instruments were used.

After 1 year, 189 patients could be evaluated. Fifty-eight patients (31%) underwent only SLNB, and 131 patients (69%) underwent ALND. Patients in the ALND group showed significantly larger changes in the range of motion in forward flexion, abduction, and abduction/external rotation; grip strength and strength of shoulder abductors; circumference of upper arm and forearm; and perceived shoulder disability in ADL compared to the SLNB group. Multivariate linear regression analysis showed that ALND could predict a decrease of range of motion in forward flexion, abduction, strength of shoulder abductors, grip strength, and shoulder-related disabilities in ADL and an increase in the circumference of the upper arm. Radiation of the axilla predicts an additional decrease in shoulder range of motion.

The objective of the studies described in **Chapter 6a and 6b** concerns phantom breast sensations (PB sensations) and phantom breast pain (PB pain) after mastectomy.

The aim of the study described in **Chapter 6a** was to assess prospectively the incidence of PB sensations and PB pain in a sample of 82 mastectomy patients and to assess how much they are bothered by PB sensations and PB pain. Therefore patients were assessed 6 weeks, 6 months, 1 year and 2 years after mastectomy, by means of a questionnaire. After 2 years, assessments of 74 patients were available.

Two years after mastectomy, PB sensations were present in 19% (n=14) of the patients and PB pain was present in 1% (n=1) of the patients. Patients were hardly bothered by PB sensations or PB pain. Over time the percentage of patients with PB sensations remained relatively stable (around 20%) but for PB pain the percentage reduced from 7% to 1%. PB sensations and PB pain were of little clinical relevance in the 2 years following mastectomy.

Aim of the study described in **Chapter 6b** was to analyze the influence of research methodology on prevalence of PB sensations and PB pain. Research design, assessment method and publication date were recorded. Data were weighted according to the number of women included in the study. Linear regression analysis was performed to analyze influences of methodology on prevalence of PB sensations and PB pain.

Of the 29 studies identified, 23 were cross-sectional and 6 were prospective. In 17 studies patients were interviewed and in 12 studies a questionnaire was used. A prospective design resulted in prevalence of PB sensations and PB pain averagely 8% lower respectively 9% higher than in cross-sectional studies. Use of an interview resulted in prevalence of PB sensations and PB pain averagely 13% lower respectively 5% lower than questionnaire use. Prevalence of PB sensations and PB pain reduces averagely with 0.08% respectively 0.13% per year since 1950.

In **Chapter 7** the intra- and interobserver reliability was investigated of indirect volume measurement that utilized surface measurements and a simplified formula derived from the formula for a frustum (Sitzia's method), as well as to compare volume determination using this method with the water displacement method.

Repeated measurements of upper-extremity limb volume were obtained by two observers on both upper extremities of 30 women with unilateral lymph edema. Volume was calculated using a simplified formula and compared with water displacement method as a "gold standard".

Results of the study showed that intra- and interobserver reliabilities of the Sitzia's method and the water displacement method were both good. Further, a strong correlation between Sitzia's method using surface measurements at 4 cm intervals and the water displacement method was found. If Sitzia's method using 4 cm and 8 cm intervals is compared to water displacement method, a relatively large standard deviation in mean difference was found, suggesting that the measures should not be used interchangeably.

The study concluded that indirect volume determination using surface measurements with 4 cm intervals with a formula for a frustum (Sitzia's method) is comparable with the water displacement method ("the gold standard"), with comparable intra- and interobserver reliabilities. Sitzia's method can be used in diagnosis and follow up measurements of lymph edema. The methods should not be used interchangeably.

Chapter 8 attends to the long-term treatment related upper limb morbidity, perceived disabilities in ADL and QOL after SLNB or ALND for breast cancer. In this prospective study, 181 patients could be evaluated after two years. 57 patients underwent SLNB (31%) and 124 patients underwent an ALND (69%). Assessments included pain, shoulder range of motion, muscle strength, arm volume, perceived shoulder disability in ADL and QOL. Identical assessment instruments were used as described in chapter 4, except arm volume was calculated by means of indirect volume determination using surface measurements with 4 cm intervals and QOL was assessed with help of the EORTC QLQ-C30 questionnaire supplemented with the EORTC Breast Module (EORTC QLQ-BR23).

After two years substantial long-term treatment-related upper-limb morbidity was observed for the whole study group. Disability in ADL increased as assessed with the SDQ and the GARS. Also significant changes were found for QOL. Physical and role functions decreased. Emotional function and symptom scales/items such as fatigue, pain, dyspnoea, constipation and financial problems increased. From the functional scales of the breast cancer module, body image decreased while future perspective increased. Also an increase of side effects and arm symptoms was found.

Several changes two years after treatment in upper-limb function (abduction and abduction/external rotation, grip strength, arm volume and numbness), ADL (GARS)

and QOL (physical and role functioning, pain, insomnia and arm symptoms) were significantly different between the SLNB group and the ALND group in favor of the first. Multivariate linear regression analysis showed that ALND could predict decrease of ROM in abduction, grip strength, ADL and physical functioning (QOL) and increase of arm volume, pain and arm symptoms score (QOL). Radiation on the axilla predicts an additional decrease in shoulder ROM and increase of arm volume. Mastectomy was a predictor for the SDQ score and QOL domains social functioning, appetite loss and body image and breast symptoms. Long-term upper limb morbidity was significantly correlated with disabilities in ADL and worsening of QOL.

Chapter 9 provides the general discussion, in which the most important findings of this thesis are addressed. Answers on the research questions formulated in the introduction are given and discussed in relation to their clinical relevance and implications. Further, weaknesses of the studies are discussed and recommendations for future research are provided.

In terms of clinical relevance, results of the study provide criteria by which patients at risk for upper limb morbidity can be determined by their treatment variables. Because the long-term effects of upper limb morbidity on QOL, integration of psycho-oncological support into the somatic treatment to ensure comprehensive care for breast cancer patients, is indicated.

General conclusions and answers on the main research questions of this thesis are:

1. In literature a significant relationship between late morbidity after treatment of early breast cancer and restrictions of daily activities and worsening of QOL is described. The strength of this relationship is weak or not given and clinical relevance is poorly investigated.
2. Significant treatment related short-term, middle-term and long-term upper limb morbidity and perceived disabilities in ADL and long-term reduction of QOL exists in breast cancer patients.
3. Treatment related upper limb morbidity, perceived disabilities in ADL and worsening of QOL up till two years after surgery is significantly less after SLNB compared to ALND.
4. In the assessment of changes in upper limb function, ADL and QOL, ALND is the most frequent found predictor of deterioration. Additional radiation on the axilla predicts a further decrease in shoulder ROM and increase of arm edema.
5. Long-term upper limb morbidity is significantly correlated with disabilities in ADL and worsening of QOL. Clinical relevance of this correlation is clearly demonstrated.

Samenvatting

Dit proefschrift heeft tot onderwerp; de therapie gerelateerde morbiditeit van de bovenste extremiteit, beperkingen in activiteiten van het dagelijkse leven (ADL) en kwaliteit van leven (KVL) bij borstkanker patiënten.

In **Hoofdstuk 1,** de introductie van het proefschrift, worden het doel, de inhoud en de belangrijkste onderzoeksvragen geformuleerd. Borstkanker therapie is vanaf het begin geassocieerd met morbiditeit van de bovenste extremiteit zoals pijn en gevoelloosheid, verminderde bewegelijkheid van de schouder, spierzwakte van arm en hand en lymfoedeem. De oksel chirurgie (okselklier dissectie of axillary lymph node dissection [ALND]) is in eerste instantie verantwoordelijk voor chronische problemen van afgenomen mobiliteit van de schouder en lymfoedeem van de arm. Aanvullende radiotherapie van de oksel kan de morbiditeit van de bovenste extremiteit laten toenemen ten gevolge van bestralingsschade aan het weefsel. In de begin negentiger jaren werd de poortwachterklier procedure (sentinel lymph node biopsy [SLNB]) geïntroduceerd ter stadiëring van de oksel en tegenwoordig is deze SLNB een uitstekend alternatief voor de ALND bij patiënten zonder klinisch aanwezige gemetastaseerde okselklieren. Onderzoek, uitgevoerd ter evaluatie van deze procedure vergeleken met de ALND, beschreef minder morbiditeit bij de SLNB. Deze onderzoeken vertoonden overeenkomstige methodologische tekortkomingen, zoals het ontbreken van een meting voorafgaand aan de behandeling en de afwezigheid van betrouwbare en valide meetinstrumenten. Tevens werd de relatie tussen behandelingsmodaliteiten en therapie gerelateerde morbiditeit, ADL en KVL slechts zeer zelden beschreven.

Dus werd het noodzakelijk een prospectieve lange termijn cohort studie uit te voeren met betrouwbare en valide meetinstrumenten naar therapie gerelateerde morbiditeit van de bovenste extremiteit, ADL en KVL bij patiënten met borstkanker, behandeld met de SLNB in vergelijking met de ALND.

Dit proefschrift behandelt de mate van therapie gerelateerde morbiditeit van de bovenste extremiteit, de relatie naar ADL en KVL, geassocieerde therapeutische variabelen, borst fantoomgevoel en borst fantoompijn na een mastectomie en de betrouwbaarheid en validiteit van een methode van indirecte volumemeting. De belangrijkste onderzoeksvragen, die in dit proefschrift worden beantwoord, zijn:

1. Wat is in de literatuur bekend over de morbiditeit van de bovenste extremiteit in relatie tot ADL en KVL bij patiënten na behandeling van borstkanker?
2. Wat zijn de korte termijn, middel termijn en langere termijn morbiditeit van de bovenste extremiteit en de ervaren beperkingen in ADL na behandeling van borstkanker?
3. Wat zijn de veranderingen in KVL twee jaar na start van borstkanker behandeling?

4. Wat zijn de verschillen tussen SLNB en ALND met betrekking tot morbiditeit van de bovenste extremiteit, de ervaren beperkingen in ADL en KVL?
5. Welke therapeutische variabelen zijn geassocieerd met morbiditeit van de bovenste extremiteit, beperkingen in ADL en vermindering van KVL?
6. Wat is de relatie tussen morbiditeit van de bovenste extremiteit, de ervaren beperkingen in ADL en KVL?

Hoofdstuk 2 beschrijft een systematische review die was uitgevoerd om de resultaten van alle studies die de chronische morbiditeit bij borstkanker patiënten in relatie tot ADL en KVL analyseerden, te evalueren. Hiertoe werd een zoektocht in de literatuur van de laatste 20 jaren (1980-2000) uitgevoerd in de database programma's MEDLINE, EMBASE, PSYCHLIT and CANCERLIT. De methodologische kwaliteit van de geselecteerde artikelen werd beoordeeld en aanvullend werden aspecten van therapie gerelateerde chronische morbiditeit en de relatie naar ADL en KVL samengevat.

Van de 1642 verzamelde artikelen voldeden 15 artikelen aan de primaire selectie criteria betreffende stadiëring van borstkanker, therapie modaliteiten, tijdsinterval tussen chirurgische behandeling en vastleggen van de chronische morbiditeit en de relatie tussen deze chronische morbiditeit en ADL en factoren van KVL. De gemiddelde methodologische kwaliteit van deze geselecteerde artikelen was beperkt. Weinig aandacht werd besteed aan betrouwbaarheid en validiteit van de meetinstrumenten en verrassend genoeg werd in slechts 2 studies een uitgangsmeting voorafgaand aan de behandeling verricht.

Zes artikelen voldeden aan éénderde van de vastgestelde methodologische kwaliteitscriteria en werden geselecteerd voor nadere analyse. Er bestond grote variabiliteit van de toegepaste meetinstrumenten zowel voor het vastleggen van stoornissen in de schouderfunctie als het meten van ADL. Tevens bestonden er geen uniforme criteria met betrekking tot stoornissen in pijn, schoudermobiliteit, oedeem of spierkracht.

Aanzienlijke variatie werd gevonden in de prevalentie van pijn (12-51%), stoornissen in de schoudermobiliteit (2-51%), oedeem (6-43%) en verminderde spierkracht (17-33%). Er werd melding gemaakt van significante relaties tussen chronische morbiditeit en beperkingen in ADL en afgenomen KVL, maar de kracht van deze relaties was laag en de klinische relevantie werd niet duidelijk beschreven.

Het doel van de studie gepresenteerd in **hoofdstuk 3** was om de functiestoornissen, beperkingen en gezondheidsgerelateerde KVL bij patiënten na behandeling van borstkanker vast te leggen, en de relatie tussen de verschillende behandelmodaliteiten, functiestoornissen, beperkingen en gezondheidsgerelateerde KVL te analyseren.

In deze retrospectieve studie werden 55 patiënten die een gemodificeerde radicale mastectomie (borstamputatie) of een segmentale mastectomie (borstsparende operatie)

met een ALND hadden ondergaan, gemiddeld 2.7 jaar na behandeling onderzocht. Functiestoornissen werden vastgelegd met behulp van metingen van de schoudermobiliteit, knijpkracht, armvolume en pijn. Beperkingen in schouderfunctie gerelateerde ADL werden vastgelegd met behulp van de Schouder Beperkingen Vragenlijst (SDQ) en gezondheidsgerelateerde KVL met behulp van de RAND 36-item Health Survey (RAND-36). De meest frequent gevonden functiestoornissen waren pijn (60%) en verminderde knijpkracht (40%). De prevalentie van gestoorde schoudermobiliteit was 16% en de prevalentie van oedeem was 15%. Gemiddelde scores voor fysiek functioneren, vitaliteit en gezondheidsperceptie van de RAND-36 waren significant lager dan die van een normgroep van vrouwen. Radiotherapie en in mindere mate chemotherapie waren significante voorspellende factoren met betrekking tot gestoorde schoudermobiliteit. Wanneer de functiestoornissen werden gebruikt om beperkingen in schouderfunctie gerelateerde ADL te voorspellen, dan verklaarde pijn 61% van de variatie in de SDQ score en schoudermobiliteit (anteflexie en exorotatie) verklaarde 12% van de variatie in SDQ score. Pijn, knijpkracht en armvolume waren significante voorspellende factoren met betrekking tot gezondheidsgerelateerde KVL in 6, 3 en 2 domeinen van de RAND-36.

Zwaktes van de uitgevoerde studie kunnen worden geformuleerd in de relatief lage responsratio en de afwezigheid van een uitgangsmeting voorafgaand aan de behandeling. Implicaties voor behandelaars in de revalidatie zijn gelegen in de relatief matige functiestoornissen waarvan pijn en afgenomen schoudermobiliteit gerelateerd zijn aan milde beperkingen in ADL en enkele domeinen van gezondheidsgerelateerde KVL.

Het onderwerp van de studie, beschreven in **hoofdstuk 4,** betreft een prospectieve analyse van de korte termijn morbiditeit van de bovenste extremiteit en de door de patiënt ervaren beperkingen in ADL na de SLNB of de ALND.

De studie includeerde 204 patiënten met stadium I/II borstkanker waarvan 198 patiënten de pre- en postoperatieve beoordelingen voltooiden; 62 patiënten met een SLNB en 136 met een ALND. Verdere chirurgische behandeling bestond uit een gemodificeerde radicale mastectomie of borstsparende chirurgie.

Armfunctie en ADL werden 1 dag voor en 6 weken na chirurgie geëvalueerd. De mate van pijn werd vastgelegd met de visual analogue scale (VAS). Actieve schouder mobiliteit werd volgens een gestandaardiseerd protocol gemeten met behulp van een goniometer. Spierkracht van de schouder-abductoren en elleboog-flexoren werd gemeten met behulp van een Citec® hand-held dynamometer en de knijpkracht werd gemeten met de Yamar® hand-held dynamometer. Omvang van de bovenarm en onderarm werd gemeten met behulp van een Gulick meetband op 10 cm proximaal van het olecranon en 15 cm proximaal van het processus styloideus. De mate van ADL werd beoordeeld door middel van de SDQ en de Groningen Activiteiten Restrictie Schaal (GARS).

Aanzienlijke therapie gerelateerde morbiditeit werd gevonden bij de gehele studiegroep. Met betrekking tot pijn, schoudermobiliteit in anteflexie, abductie en abductie/exorotatie, kracht van schouder-abductoren en elleboog-flexoren en de ervaren beperkingen in ADL waren de gevonden veranderingen significant. Zes weken na de chirurgische behandeling werden bij 14 patiënten in de SLNB groep (23 %) en in 119 patiënten in de ALND groep (87%) gevoelsverlies van de huid waargenomen. De vermindering van de schoudermobiliteit in anteflexie, abductie, abductie/exorotatie, de knijpkracht, de kracht van de schouder-abductoren en elleboog-flexoren en de toename van de ervaren beperkingen gemeten met de GARS was significant groter in de ALND groep in vergelijking met de SLNB groep. ALND en in mindere mate mastectomie waren significante factoren in de voorspelling van morbiditeit van de bovenste extremiteit en ervaren beperkingen van ADL (GARS). Stoornissen zoals pijn, verminderde schoudermobiliteit en spierkrachtverlies waren significant gecorreleerd aan ervaren beperkingen in ADL 6 weken na de chirurgische behandeling.

Hoofdstuk 5 behandelt het zelfde onderwerp als hoofdstuk 4 maar hier heeft de studie een vervolg duur van 1 jaar na chirurgische behandeling. Er werd gebruik gemaakt van identieke beoordelingsmeetinstrumenten als in hoofdstuk 4.

Na 1 jaar konden 189 patiënten worden geëvalueerd. Achtenvijftig patiënten (31%) ondergingen SLNB en 131 patiënten (69%) ondergingen een ALND. Patiënten die behoorden tot de ALND groep vertoonden significant meer verandering in de schoudermobiliteit in anteflexie, abductie en abductie/exorotatie, de knijpkracht en kracht van schouder-abductoren, de omvang van bovenarm en onderarm en de ervaren beperkingen in ADL, in vergelijking tot de patiënten behorend tot de SLNB groep. Met multivariaat lineaire regressie analyse werd aangetoond dat ALND een voorspellende factor is voor een afname van de mobiliteit in anteflexie en abductie, de kracht van schouder-abductoren, de knijpkracht en schouder gerelateerde ADL en voor een toename van de omvang van de bovenarm. Radiotherapie van de oksel heeft een voorspellende waarde met betrekking tot een additionele afname van de schoudermobiliteit.

De onderwerpen van de studies die beschreven zijn in **Hoofdstuk 6a en 6b** betreffen borst fantoomgevoel en borst fantoompijn na mastectomie.

Het doel van de studie gepresenteerd in **hoofdstuk 6a** was om prospectief de incidentie van borst fantoomgevoel en borst fantoompijn te registreren in een cohort van 82 mastectomie patiënten en te onderzoeken in welke mate zij gehinderd werden door fantoomgevoel en fantoompijn. Daartoe werden de patiënten 6 weken, 6 maanden, 1 jaar en 2 jaar na de mastectomie beoordeeld met behulp van een vragenlijst. Twee jaar na mastectomie waren van 74 patiënten gegevens beschikbaar voor onderzoek. Twee jaar na mastectomie was borst fantoomgevoel aanwezig in

19% (n=14) van de patiënten en borst fantoompijn was aanwezig in 1% (n=1) van de patiënten. De betreffende patiënten werden nauwelijks gehinderd door borst fantoomgevoel of fantoompijn. Het percentage patiënten met borst fantoomgevoel bleef gedurende de vervolg periode van 2 jaar relatief stabiel (ca. 20%) terwijl het percentage patiënten met borst fantoompijn in die tijdsperiode afnam van 7% naar 1%. Borst fantoomgevoel en borst fantoompijn hebben weinig tot geen klinische relevantie in patiënten tot 2 jaar na een mastectomie.

Het doel van de studie gepresenteerd in **hoofdstuk 6b** was te onderzoeken in hoeverre onderzoeksmethodologie de uitkomsten met betrekking tot prevalentie van borst fantoomgevoel en borst fantoompijn beïnvloedden. Het onderzoeksdesign, de beoordelingsmethode en het jaar van publicatie van een studie werden geregistreerd. De uitkomsten van de studies werden gewogen naar het aantal geïncludeerde patiënten. Om de invloed van de gebruikte methodologie op de prevalenties van borst fantoomgevoel en borst fantoompijn te analyseren werd een lineaire regressie analyse toegepast.

Van de 29 beoordeelde studies, waren er 23 cross-sectioneel en 6 prospectief. Interviews werden toegepast in 17 studies terwijl in 12 studies een vragenlijst werd gebruikt. Een prospectieve design resulteerde in een gemiddeld 8% lagere prevalentie van borst fantoomgevoel, respectievelijk 9% hogere prevalentie van borst fantoompijn ten opzichte van studies met een cross-sectioneel design. Het gebruik van een interview resulteerde in gemiddeld 13% respectievelijk 5% lagere prevalenties van borst fantoomgevoel en borst fantoompijn in vergelijking tot het gebruik van een vragenlijst. De prevalentie van borst fantoomgevoel en borst fantoompijn verminderen gemiddeld met 0.08% respectievelijk 0.13% per jaar sinds 1950.

Hoofdstuk 7 betreft een studie met als doel de intrabeoordelaar en interbeoordelaar betrouwbaarheid van een indirecte volumemeting welke gebruik maakt van omtrekmetingen en een gesimplificeerde formule voor een kegelvorm (Sitzia methode) te onderzoeken, en tevens deze methode te vergelijken met de volumemeting met behulp van de waterverplaatsing methode.

Bij 30 vrouwen met eenzijdig lymfoedeem werden door 2 onderzoekers herhaalde volumemetingen van de bovenste extremiteit uitgevoerd. Met behulp van de gesimplificeerde formule voor een kegelvorm werd het volume berekend en vergeleken met de 'gouden standaard', de waterverplaatsing methode. De onderzoeksresultaten toonden zowel voor de 'Sitzia methode' als de waterverplaatsing methode goede intra- en interbeoordelaar betrouwbaarheid aan. Tevens werd een sterke relatie gevonden tussen de 'Sitzia methode' met omtrekmetingen om de 4 cm en de waterverplaatsing methode. Bij de vergelijking van de 'Sitzia methode' met omtrekmetingen om de 4 cm en 8 cm met de waterverplaatsing methode, werden relatief grote standaard deviaties gevonden in het gemiddelde verschil. Dit suggereert dat de beide methoden niet afwisselend toegepast dienen te worden.

De studie concludeert dat de 'Sitzia methode' vergelijkbaar is met de 'gouden standaard' de waterverplaatsing methode, met een vergelijkbare intra- en interbeoordelaar betrouwbaarheid. De Sitzia methode kan worden gebruikt bij diagnose en vervolgmetingen van lymfoedeem.

Hoofdstuk 8 behandelt de langere termijn therapie gerelateerde morbiditeit van de bovenste extremiteit, de ervaren beperkingen in ADL en KVL na SLNB of ALND bij borstkanker. In deze prospectieve studie konden 181 patiënten geëvalueerd worden na 2 jaar. 57 patiënten ondergingen SLNB (31%) en 124 patiënten ondergingen ALND (69%). Pijn, schoudermobiliteit, spierkracht, armvolume, ADL en KVL werden beoordeeld. Dezelfde meetinstrumenten werden gebruikt als beschreven in hoofdstuk 4, behalve dat in dit hoofdstuk het armvolume wordt berekend volgens de 'Sytzia methode' en KVL wordt vastgelegd met behulp van de EORTC QLQ-C30 vragenlijst aangevuld met de EORTC borst module (EORTC QLQ-BR23).

Na 2 jaar werd voor de gehele studie groep een aanzienlijke therapie gerelateerde morbiditeit van de bovenste extremiteit aangetoond. Beperkingen in ADL, vastgelegd met de SDQ en de GARS namen toe. Tevens werden significante veranderingen in KVL gevonden. De domeinen 'fysiek functioneren' en 'rol functioneren' verslechterden. Het 'emotioneel functioneren' verbeterde en symptoom scores zoals vermoeidheid, pijn, dyspneu, obstipatie en 'financiële problemen' namen toe. Van de functionele domeinen van de borst module verslechterde het domein 'lichaamsbeeld' terwijl 'toekomstperspectief' verbeterde. Tevens werd een toename gevonden van de items betreffende 'bijwerkingen van systeembehandeling' en armsymptomen.

Meerdere veranderingen, 2 jaar na chirurgische behandeling, in functioneren van de bovenste extremiteit (abductie en abductie/exorotatie, knijpkracht, armvolume en gevoelstoornissen), ADL (GARS) en KVL ('fysiek' en 'rol functioneren', pijn, slapeloosheid en armsymptomen) waren significant verschillend tussen de SLNB groep en de ALND groep, ten gunste van de eerste. Multivariaat lineaire regressie analyse toonde aan dat ALND een voorspellende factor is voor een afname van schoudermobiliteit in abductie, knijpkracht, ADL en het domein 'fysiek functioneren' van KVL en voor een toename van het armvolume, pijnscore en armsymptomen score (KVL). Radiotherapie van de oksel is gerelateerd aan een verdere afname van de schoudermobiliteit en een toename van het armvolume. Een mastectomie heeft een voorspellende waarde voor de SDQ score en de domeinen 'sociaal functioneren', eetlustverlies, lichaamsbeeld en borstsymptomen van KVL. Langere termijn morbiditeit van de bovenste extremiteit is significant gecorreleerd met beperkingen in ADL en verslechtering van KVL.

Hoofdstuk 9 levert de algemene discussie waarin de meest belangrijke bevindingen van dit proefschrift onder de aandacht worden gebracht. De in de introductie geformuleerde onderzoeksvragen worden beantwoord en bediscussieerd in relatie tot

de klinische relevantie en implicaties. Tevens worden de zwaktes van de studies bediscussieerd en aanbevelingen voor toekomstig onderzoek gedaan

In termen van klinische relevantie, leverden de resultaten van de studies criteria, waardoor patiënten met een risico voor het ontwikkelen van morbiditeit van de bovenste extremiteit vanuit de behandeling variabelen onderkend kunnen worden. Vanwege het langere termijn effect van morbiditeit van de bovenste extremiteit op KVL, dient integratie van psycho-oncologische ondersteuning binnen de somatisch gerichte behandeling plaats te vinden, om volledige zorg voor borstkanker patiënten te verzekeren.

Algemene conclusies en antwoorden op de belangrijkste onderzoeksvragen van dit proefschrift zijn:

1. In de literatuur wordt een significante relatie beschreven tussen langere termijn morbiditeit ontstaan na behandeling van borstkanker en beperkingen in dagelijkse activiteiten en verslechtering van KVL. De sterkte van deze relatie is laag of wordt niet beschreven en de klinische relevantie is slecht onderzocht.
2. Significante korte termijn, middel termijn en langere termijn therapie gerelateerde morbiditeit van de bovenste extremiteit en ervaren beperkingen in ADL en langere termijn vermindering van KVL zijn aanwezig bij borstkanker patiënten.
3. Therapie gerelateerde morbiditeit van de bovenste extremiteit, beperkingen in ADL en verslechtering van KVL tot en met 2 jaar na chirurgie is significant minder aanwezig na SLNB in vergelijking met ALND.
4. Bij de beoordeling van de veranderingen in functie van de bovenste extremiteit, ADL en KVL, is ALND de meest frequent voorkomende voorspeller van verslechtering. Radiotherapie op de oksel is geassocieerd met een additionele vermindering van de schoudermobiliteit en toename van lymfoedeem.
5. Langere termijn morbiditeit van de bovenste extremiteit is significant gecorreleerd aan beperkingen in ADL en verslechtering van KVL. De klinische relevantie van deze correlatie is duidelijk gedemonstreerd.

DANKWOORD

Dankwoord

Dit proefschrift is het resultaat van de samenwerking tussen de afdeling Revalidatie, de afdeling Chirurgische Oncologie en de afdeling Radiotherapie van het Universitair Medisch Centrum Groningen, de afdeling Revalidatie en de afdeling Chirurgie van het Martini Ziekenhuis Groningen en het Noordelijk Centrum voor Gezondheidsvraagstukken. Meerdere mensen hebben direct of indirect een bijdrage geleverd aan dit proefschrift. Dank ben ik verschuldigd aan:

Prof. W.H. Eisma, Willem, eerste promotor, pater familias van de Revalidatiegeneeskunde (in ieder geval in Groningen), mijn tutor.
Prof. dr. H.J. Hoekstra, Harald, tweede promotor, kritisch en dus lastig, echter constructief bijdragend in het gehele proces van onderzoek.
Prof. dr. J.H.B. Geertzen, Jan, derde promotor, vriend, drijver, collega maar bovenal de beste sparring partner die ik me kan wensen in vele revalidatie zaken, laat het in de toekomst ook zo zijn.
Prof. dr. J.W. Groothoff, Johan, vierde promotor, stimulator, richting gevend en niet van de wijs te brengen.
Dr. P.U. Dijkstra, Pieter, co-promotor, methodoloog, statisticus maar bovenal een redenaar, onze discussies hebben mij en het onderzoek gevormd.
Dr. W.V. Dolsma, Wil, lid begeleidingscommissie, ondersteunend in de voor mij onbekende radiotherapeutische aspecten.
Mw. Prof. Dr. E. Lindeman, Prof. Dr. R. Sanderman en Prof. Dr. T. Wobbes voor de bereidwilligheid zitting te nemen in de beoordelingscommissie.
Jannie Kootstra, research nurse (destijds), de beste die een onderzoeker zich kan wensen, tevens een geweldig persoon.
Gerda Yntema en Kees Meyer, nurse practitioners bij de Mamma Care in het MZH en het UMCG, voor het inlichten van de patiënten en mij.
Het secretariaat polikliniek Revalidatie MZH, Siska, Ellen en Linda voor de afspraken, de onderzoekskamer en een kop koffie ten tijde van het onderzoek.
Het secretariaat polikliniek Revalidatie UMCG, voor de plezierige samenwerking.
Alle participerende patiënten, voor de genomen moeite om tijdens en na het langdurige behandelproces mee te werken aan de metingen.
Prof. dr. J. de Vries en Dr. P. Baas, Jaap en Peter, chirurgen, kritische lezers en medeauteurs.
Prof. dr. B.G. Szabo, begeleider in aanvang en medeauteur van hoofdstuk 2.
Truus van Ittersum, voor de meer dan volledige search strategie bij hoofdstuk 2 en het mij op de hoogte houden van relevante literatuur.
Rolanda Debreczeni en Douglas Robinson, onderzoekers en medeauteurs van hoofdstuk 3.

Reinout Meijer en Jolien Bosmans, onderzoekers en medeauteurs van hoofdstuk 7.
Sjoukje Hiemstra, collega revalidatiearts, jouw handen maken prachtige kunst.
Collegae revalidatieartsen van de afdeling Revalidatie van het Martini Ziekenhuis en het UMCG, voor de goede, prettige en stimulerende samenwerking.
Inge Zweerts de Jong-Veeze, secretaresse van 'De Professoren' en zonder dat ze het wisten ook van mij, vriendin, onmisbaar, nog steeds.
Paranimfen, Cees Buren en Rienk Dekker, Cees, brother in arms, chronisch vriend, blij en vereerd om jou erbij te hebben. Rienk, collega en vriend, dezelfde tijdgeest en dus begrip zonder te vragen, ik ben blij met jou als paranimf.
Pa en Ma, voor alles, ik weet dat jullie er graag bij hadden willen zijn.

Marina, Loes, Imre, Ellen en Koen, niet voor een bijdrage aan dit proefschrift, wel voor al het andere.

Northern Centre for Healthcare Research (NCH)

This thesis is published within the research program **Rehabilitation Programs Research** of the Northern Centre for Healthcare Research. More information regarding the institute and its research can be obtained from our internet site: www.med.rug.nl/nch.

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